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TESIS DOCTORAL:

EFECTIVIDAD CLÍNICA DE LA OSTEOPATÍA. JUICIO CRÍTICO DE LA EVIDENCIA

Presentada por Luis Ceballos Laita para optar al grado
de
Doctor por la Universidad de Valladolid

Dirigida por:
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Efectividad clínica de la osteopatía. Juicio crítico de la evidencia

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TESIS POR COMPENDIO DE PUBLICACIONES

La presente tesis doctoral con título “Efectividad clínica de la osteopatía. Juicio crítico de la evidencia” representa un compendio de cuatro estudios publicados en revistas científicas con índice de impacto incluido en la relación de revistas del J*ournal Citation Reports* (JCR).

A continuación, se detallan las referencias completas de cada una de las publicaciones que componen el trabajo:

1. Ceballos-Laita L, Jiménez-Del-Barrio S, Carrasco-Uribarren A, Medrano-de-la-Fuente R, Robles-Pérez R, Ernst E. Is Osteopathic Manipulative Treatment Clinically Superior to Sham or Placebo for Patients with Neck or Low-Back Pain? A Systematic Review with Meta-Analysis. Diseases. 2024 Nov 8;12(11):287. doi: 10.3390/diseases12110287. PMID: 39589961; PMCID: PMC11593019.

2. Ceballos-Laita L, Ernst E, Carrasco-Uribarren A, Esteban-Tarcaya G, Mamud-Meroni L, Jiménez-Del-Barrio S. Is visceral osteopathy therapy effective? A systematic review and meta-analysis. International Journal of Osteopathic Medicine. 2024 Jul 54:100729. doi: 10.1016/j.ijosm.2024.100729

3. Ceballos-Laita L, Ernst E, Carrasco-Uribarren A, Cabanillas-Barea S, Esteban-Pérez J, Jiménez-Del-Barrio S. Is Craniosacral Therapy Effective? A Systematic Review and Meta-Analysis. Healthcare (Basel). 2024 Mar 18;12(6):679. doi: 10.3390/healthcare12060679. PMID: 38540643; PMCID: PMC10970181.

4. Mamud-Meroni L, Tarcaya GE, Carrasco-Uribarren A, Rossettini G, Flores-Cortes M, Ceballos-Laita L. "The Dark Side of Musculoskeletal Care": Why Do Ineffective Techniques Seem to Work? A Comprehensive Review of Complementary and Alternative Therapies. Biomedicines. 2025 Feb 6;13(2):392. doi: 10.3390/biomedicines13020392. PMID: 40002804; PMCID: PMC11853516.

AGRADECIMIENTOS

A mi hija, Martina

1 ÍNDICE

ABREVIATURAS

CC	Colaboración Cochrane
FBE	Fisioterapia Basada en la Evidencia
NCCAM	Instituto Nacional para Medicina Complementaria y Alternativa
NNCIH	Centro Nacional de Salud Complementaria e Integrativa
OAM	Oficina de Medicina Alternativa
REDETS	Red Española de Agencias de Evaluación de Tecnología y Prestaciones del Sistema Nacional de Salud.

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INTRODUCCIÓN

1 INTRODUCCIÓN

1.1. FISIOTERAPIA BASADA EN LA EVIDENCIA

La Fisioterapia basada en la evidencia (FBE) es el modelo de actuación que supone la integración de los avances científicos y del conocimiento en los contextos sociosanitarios y en la práctica clínica habitual. Dentro del concepto de FBE, la práctica clínica basada en la evidencia es el que más ha proliferado en el ámbito profesional y clínico para dar respuesta a las múltiples cuestiones que los fisioterapeutas abordan en su actividad profesional (Gómez Conesa, 2010).

La aplicación clínica de la evidencia requiere de su conocimiento previo y su utilización de forma lógica en la toma de decisiones. Lo que quiere decir que, el fisioterapeuta debe utilizar los resultados de las investigaciones clínicas para tomar decisiones con sus pacientes, así como reemplazar, modificar o enriquecer métodos, técnicas y procedimientos de actuación, planes, protocolos y programas de atención. De este modo, la FBE ayuda a optimizar el tiempo del fisioterapeuta tanto en la realización del diagnóstico, como en el diseño de tratamientos o estrategias preventivas y/o promotoras de la salud, disminuyendo de este modo la incertidumbre en los escenarios clínicos.

La aplicación clínica de la FBE se basa en diferentes pasos:

1. Buscar las preguntas clínicas a responder.
2. Localizar las evidencias de mayor solidez con las cuales contestar a las preguntas.
3. Evaluar críticamente la evidencia para conocer su aplicabilidad en el contexto clínico en cuestión.
4. Aplicar las conclusiones a la situación clínica considerando los riesgos e incertidumbre frente a los beneficios y su efectividad, teniendo en cuenta las consideraciones del paciente y sus necesidades emocionales.

En este sentido, se debe buscar siempre los estudios que presenten un mayor nivel de evidencia. De forma general los tipos de diseño se suelen clasificar siguiendo una categorización y jerarquización en función del nivel de evidencia (tabla 1) (Seco Calvo, 2022).

Tabla 1. Categorización y jerarquización de los tipos de estudio y su nivel de evidencia.

Nivel de evidencia	Tipo de estudio
Nivel 1	Ensayos clínicos aleatorios controlados de alta calidad, con o sin diferencias significativas, pero con intervalos de confianza estrechos. Revisiones sistemáticas con o sin meta-análisis de ensayos clínicos de nivel 1 con homogeneidad de resultados.
Nivel 2	Ensayos clínicos controlados de menor calidad Estudios prospectivos comparativos Revisiones sistemáticas con o sin meta-análisis de ensayos clínicos de nivel 1 o 2 con resultados inconsistentes.
Nivel 3	Estudios de casos y controles Revisiones sistemáticas de estudios de nivel 3
Nivel 4	Series de casos
Nivel 5	Opiniones de expertos

Información extraída del libro Fisioterapia Comunitaria y Salud Publica (Seco Calvo, 2022).

Por lo tanto, para poder responder a las preguntas clínicas planteadas con la mayor certeza de la evidencia posible, lo más adecuado sería tratar de localizar siempre las revisiones sistemáticas y metaanálisis, así como los ensayos clínicos originales, siempre y cuando no exista una guía clínica completa y exhaustiva acerca del tema.

1.1.1. Modelo Cochrane como forma de evaluar la evidencia a través de revisiones meta-analíticas

A pesar de esto, la aplicación de la FBE no es a priori sencilla, principalmente debido a que en las últimas décadas se ha producido un crecimiento exponencial de la investigación en Fisioterapia, lo cual genera una serie de eventos a considerar:

1) Disminución de la vida temporal de los conocimientos y vigencia de las fuentes.

2) Aparición de evidencia de dudosa calidad metodológica.

3) Exigencia de un nivel de actualización que pocas veces está al alcance real de los profesionales clínicos.

Para minimizar estos problemas cabe destacar la labor de la Colaboración Cochrane (CC) en el ámbito de la evidencia científica sobre los efectos de las intervenciones en el ámbito sanitario. La CC es una organización internacional independiente y sin ánimo de lucro que tiene como objetivo preparar, coordinar, actualizar y promover la realización de revisiones sistemáticas con metaanálisis y el acceso a sus resultados por parte de los profesionales interesados en conocer dichos datos para ayudar en las tomas de decisiones en la atención sanitaria (De Silva et al., 2001). La CC toma su nombre como tributo a Archie Cochrane, quien propuso en los 70s "*una revisión crítica de todos los ensayos clínicos controlados relevantes, actualizada periódicamente y hecha por especialidades"* enfatizando la importancia de sustentar la práctica clínica sanitaria en la mejor evidencia científica disponible.

De este modo, la realización de revisiones sistemáticas con meta-análisis rigurosos siguiendo el modelo descrito por la CC favorece el aumento de la vida temporal de los conocimientos y sus fuentes, valora la calidad metodológica y los riesgos de sesgo de los estudios primarios, y reduce la exigencia de actualización a un único articulo científico, haciendo así más sencilla la aplicación clínica de la FBE.

1.1.2. Metodología Cochrane

La metodología para realizar una revisión sistemática con meta-análisis aparece descrita en el *Cochrane Handbook for Systematic Reviews of Interventions* cuya última actualización fue en el mes de agosto de 2023 (Higgins et al., 2019).

Este libro se encuentra disponible para su lectura en abierto en inglés en la propia página web de la CC (https://training.cochrane.org/handbook/current), y explica paso por paso cómo realizar de forma correcta una revisión sistemática con o sin meta-análisis.

1.1.3. Sesgos metodológicos en ensayos clínicos

Según la CC, un sesgo se define como un error sistemático o una desviación de la verdad. Los sesgos pueden dar lugar tanto a la subestimación como a la sobreestimación de un verdadero efecto de una intervención concreta. Sin embargo, no se debe utilizar el término sesgo en un ensayo clínico debido a que no es posible conocer en qué medida el sesgo ha

afectado a los resultados de un estudio, o si ha afectado siquiera, por eso se utiliza de una forma más apropiada el término riesgo de sesgo (Higgins et al., 2023; Page et al., 2023).

A pesar de no saber en qué medida o dirección tiene influencia un sesgo, se ha descrito que es más probable que estudios más rigurosos presenten resultados más cercanos a la verdad. Entre los principales sesgos que se encuentran en los ensayos clínicos destacan:

- Sesgo de selección

Este sesgo se refiere a las diferencias entre las características iniciales de los grupos que se comparan. Para evitar estas diferencias, los participantes deben ser asignados a los grupos de intervención mediante un proceso al azar, es decir, aleatorio. Y, además, se debe evitar el conocimiento previo de esta asignación, es decir, generar una ocultación de la secuencia de aleatorización. Por lo tanto, este proceso debería llevarse a cabo de forma previa al reclutamiento del primer paciente y por parte de una persona ajena (Higgins et al., 2023; Page et al., 2023).

- Sesgo de realización

Este sesgo se refiere a las diferencias en la asistencia que se dispensa a los grupos. Para evitar estas diferencias se debe generar un cegamiento de los participantes y del personal del estudio. Este hecho puede reducir el riesgo de conocer por parte de pacientes y personal de estudio a qué grupo se asignó a cada participante. De esta manera no se generan expectativas positivas o negativas asociadas al tipo de intervención recibida por parte del paciente, y los terapeutas aseguran que los grupos comparados reciben una cantidad similar de atención (Higgins et al., 2023; Page et al., 2023).

Es de destacar que, en el ámbito de la Fisioterapia, el cegamiento del terapeuta no es posible y no por eso debe devaluarse la calidad, pero tampoco considerarse que se está libre del sesgo derivado del conocimiento de la intervención (Kamper, 2018).

- Sesgo de detección

Este sesgo se refiere a las diferencias entre grupos en la forma en la que se obtuvieron los datos de resultados. Para evitar estas diferencias se debe enmascarar o cegar a los evaluadores y utilizar herramientas validadas y fiables para el reporte de los datos de las variables dependientes. Este enmascaramiento evita que los evaluadores generen valoraciones subjetivas a favor del grupo que consideran superior, y evita la utilización de

herramientas cuyas propiedades psicométricas no han sido testadas (Higgins et al., 2023; Page et al., 2023).

Este sesgo es de vital importancia cuando las variables que se registran son subjetivas y autorreportadas, debido a que es el propio paciente el que valora sus sensaciones. Por lo que, si el paciente no está cegado, tampoco se considera que lo esté el evaluador (de Morton, 2009).

- Sesgo de desgaste

Este sesgo se refiere a las diferencias entre grupos en los abandonos del estudio o en los datos de desenlace incompletos. El porcentaje de abandonos se considera motivo de sesgo cuando los datos están disponibles para menos del 95% de los participantes incluidos. Para evitar estas diferencias se deben realizar *análisis por intención de tratar* de los datos disponibles (Higgins et al., 2023; Page et al., 2023).

En el caso de los abandonos, es de vital importancia conocer si se han dado de la misma manera en los diferentes grupos de intervención, o uno de ellos ha acarreado más pérdidas que los otros, lo que podría conllevar a diferentes desenlaces, desde el error en el enmascaramiento de los participantes hasta una terapia que empeora la situación clínica.

No se deben confundir la exclusión de participantes con los abandonos. En la exclusión de participantes, los datos están disponibles, pero no son incorporados al análisis porque se ha incumplido algún criterio de inclusión o cumplido algún criterio de exclusión.

- Sesgo de informe o notificación

Este sesgo se refiere a las diferencias entre los resultados presentados y no presentados. Estas diferencias se evitan publicando o registrando de manera prospectiva el protocolo del ensayo clínico. De este modo, los resultados a reportarse deben ser los mismos que se presentaron en el protocolo (Higgins et al., 2023; Page et al., 2023).

Puede considerarse como sesgo de informe o notificación la medición de múltiples formas diferentes o el análisis estadístico de múltiples formas diferentes de una variable dependiente, ya que es más frecuente describir y publicar diferencias estadísticamente significativas. Este sesgo es probablemente el que más pueda afectar a los resultados del estudio.

- Otros sesgos

Existen otros sesgos que deben tenerse en cuenta que no son específicos de los ensayos clínicos paralelos como (Higgins et al., 2023; Page et al., 2023):

  - Reclutamiento adicional de participantes en un subgrupo que muestra más beneficio.
  - Contaminación de la muestra por la falta de control farmacológico, dietario o físico.
  - Tendencia editorial a publicar únicamente resultados positivos acerca de un tema, sobreestimando el efecto de una intervención y pudiendo crear una tendencia falso-positivo.
  - Conflictos de interés o fraude.

1.2. TERAPIAS COMPLEMENTARIAS Y ALTERNATIVAS

En un punto diametralmente opuesto al de la FBE se encuentran las terapias complementarias y alternativas. Estas terapias se definen como "*un conjunto diverso de sistemas, prácticas y productos médicos y de atención de la salud que no se considera actualmente parte de la medicina convencional*" y suelen presentar como característica un limitado número de ensayos clínicos respaldando sus hipótesis o métodos de prueba para evaluar sus resultados en grupos de pacientes debido a que se comenzaron considerando "ajenas" a las prácticas basadas en la evidencia (Clarke et al., 2015).

Actualmente esta situación ha cambiado radicalmente, habiéndose fundado 30 revistas relacionadas con las terapias complementarias y alternativas y agrupándose en una categoría específica dentro del *Journal Citation Reports* de la base de datos *Web of Science* denominada *Integrative and Complementary Medicine*.

Tanto las terapias complementarias como las alternativas pueden llegar a ser completamente diferentes. Por un lado, las complementarias aceptan varios modelos de enfermar, y están abiertas a su uso junto con las terapias convencionales basadas en la evidencia. En el otro extremo, las alternativas contemplan un modelo de enfermar único que quiere explicar toda la complejidad de la salud y de la enfermedad (Borrel i Carrió, 2005; Nogales-Gaete, 2004; Patiño-Restrepo, 2006). Entre los ejemplos más claros cercanos a la Fisioterapia podemos encontrar la osteopatía y la ley de la arteria; la

quiropraxia y la ley del nervio; o el reiki y los bloqueos de los canales energéticos. Este tipo de terapias suelen rehuir la verificación y la falsación, entendiendo como verificación la plausibilidad biológica de sus hipótesis y como falsación admitir que si sus efectos no son superiores a un placebo no son técnicas basadas en la evidencia.

La clasificación más utilizada para estas terapias es la propuesta por el Centro Nacional de Salud Complementaria e Integrativa (NCCIH), previamente denominado como Instituto Nacional para Medicina Complementaria y Alternativa (NCCAM), y anteriormente denominado como la Oficina de Medicina Alternativa (OAM), en Estados Unidos, que describe cuatro categorías:

1. Sistemas médicos alternativos
    a. Homeopatía
    b. Naturopatía
    c. Acupuntura
    d. Medicina tradicional china
    e. Método Ayurveda
2. Enfoque sobre la mente y el cuerpo
    a. Meditación
    b. Oración
    c. Curación mental
3. Terapias biológicas
    a. Fitoterapia
4. Métodos de manipulación y basados en el cuerpo
    a. Osteopatía
    b. Quiropraxia
    c. Reflexología
5. Terapias sobre la base de la energía
    a. Electromagnetismo
    b. Reiki

Siguiendo los mismos datos de estos centros de Estados Unidos, las diez terapias complementarias y alternativas más utilizadas se encuentran, por orden de preferencia (Clarke et al., 2015):

1. **Productos naturales**: sustancias de origen vegetal, mineral o animal utilizadas para prevenir o mejorar diferentes aspectos relacionados con la salud:

2. **Respiración profunda**: técnica de inhalación controlada para reducir el estrés y la ansiedad.
3. **Yoga, Tai Chi, o Qi Gong**: prácticas de origen asiático que combinan movimiento, respiración y meditación.
4. **Osteopatía y quiropraxia**: terapias manuales basadas en la palpación y el tratamiento manual para mantener o mejorar la alineación y movilidad del cuerpo.
5. **Meditación**: practica de la concentración para controlar la mente y mejorar el bienestar.
6. **Masaje**: Movilización y manipulación de los tejidos blandos para aliviar tensión, mejorar la circulación y promover la relajación.
7. **Dietas esenciales**: Alimentación basada en nutrientes fundamentales.
8. **Homeopatía**: Uso de dosis mínimas de sustancias activas diluidas en agua para el tratamiento de enfermedades.
9. **Relajación progresiva**: técnica de liberación de tensión y de control del estrés mediante la contracción de grupos musculares y su posterior relajación.
10. **Imágenes guiadas**: Visualización dirigida para inducir calma, mejorar el estado emocional y favorecer la curación.

La clasificación de estas terapias como alternativas o complementarias básicamente dice que ninguno de estos métodos ha sido sometido a estudios científicos rigurosamente diseñados y ejecutados, cuyas preguntas esenciales (como su plausibilidad biológica) aún deben de responderse, como si lo han hecho las terapias que han pasado a formar parte de la FBE. Cuando estas terapias responden favorablemente al método científico, son eliminadas de las listas de terapias complementarias y alternativas e introducidas en el elenco de técnicas basadas en la evidencia, como por ejemplo las terapias cognitivo-conductuales (Nogales-Gaete, 2004; Patiño-Restrepo, 2006).

1.2.1. Complementario o alternativo no es equivalente a pseudoterapia

La inclusión de una terapia en el bloque de complementarias y/o alternativas no significa ni que sea eficaz ni es sinónimo de ineficacia. Ciertas terapias generan un efecto positivo en los pacientes, pero no hay estudios que corroboren si esas mejorías son debidas al efecto específico de la técnica o un mero efecto placebo (Mamud-Meroni et al., 2025).

Algunas terapias, como por ejemplo el yoga, pueden tener cierto soporte de evidencia científica que corrobore que puedan ser utilizadas como complemento de otras técnicas basadas en la evidencia para el manejo de ciertas patologías. Por el contrario, otras como la homeopatía han sido desestimadas desde su fabricación farmacológica por su falta de plausibilidad biológica.

De este modo, según el Ministerio de Sanidad de España, se debe considerar como pseudoterapia a la sustancia, producto, actividad o servicio con pretendida finalidad sanitaria que no tenga soporte en el conocimiento ni evidencia científicos que avale su eficacia y su seguridad (Gobierno de España, 2018).

Desde un punto de vista menos regulador y más científico, Fasce y Picó (Fasce & Picó, 2019) expusieron una serie de criterios que ayudan a identificar una pseudociencia:

- Suele ser presentada de manera formal como un conocimiento científico, pero abarca un aspecto considerado fuera de los dominios de la ciencia actual.
- Usa procedimientos que son deficientes, que no corresponden con el método científico o que no pueden ser comprobados por este método.
- No está apoyada por la evidencia científica.

Existen otras formas de categorización que implican una lectura en mayor profundidad de las terapias, como es la demarcación de Pigliucci (Pigliucci & Boudry, 2013), el cual considera tanto la plausibilidad biológica como el conocimiento empírico y realiza una clasificación en cuatro tipos de ciencia (Figura 1).

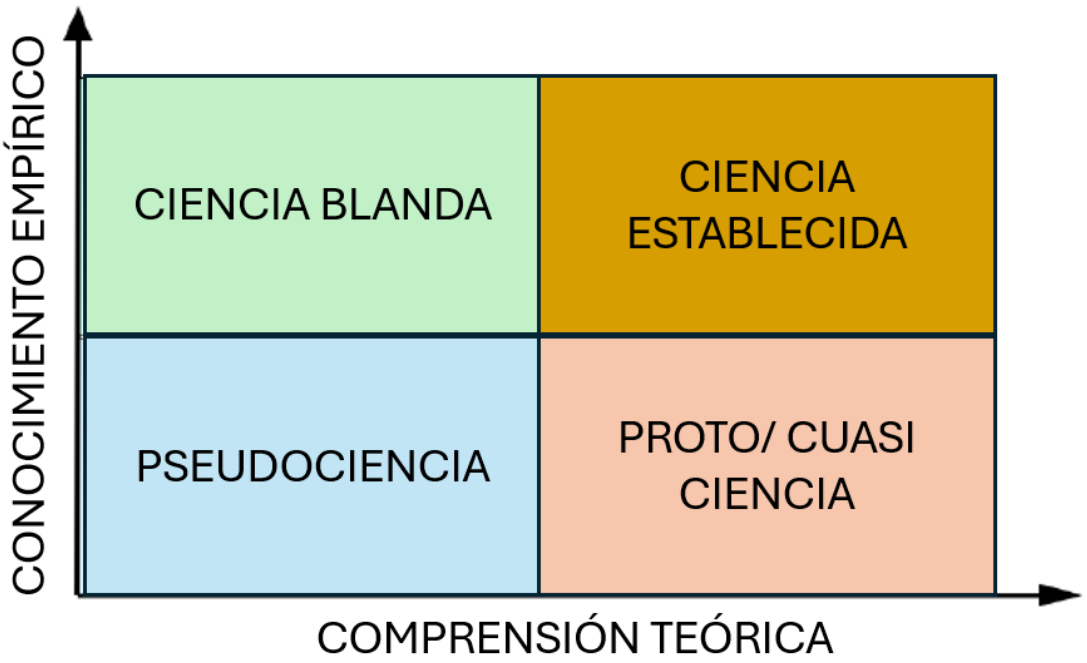

Figura 1. Filosofía de la pseudociencia. Traducido de Pigluicci (Pigliucci & Boudry, 2013).

Acorde a esta clasificación se definen las siguientes categorías:

- **Ciencia establecida** (color naranja): se refiere a la que ha mostrado una plausibilidad biológica y presenta un cuerpo de conocimiento empírico.
- **Protociencia** (color marrón): se refiere a la que ha mostrado una plausibilidad biológica pero falta de cuerpo de conocimiento empírico.
- **Ciencia blanda** (color azul): se refiere a la que ha mostrado conocimiento empírico, pero no plausibilidad biológica.
- **Pseudociencia** (color verde): se refiere a la que no ha mostrado ni plausibilidad biológica ni conocimiento empírico.

1.2.2. Pseudoterapias a estudio en el ámbito de la Fisioterapia en España

En el año 2018, el Ministerio de Sanidad, Consumo y Bienestar Social junto con el Ministerio de Ciencia, Innovación y Universidades, liderados por Dña. María Luisa Carcedo y D. Pedro Duque, respectivamente, presentaron el Plan para la protección de la salud frente a pseudoterapias (Gobierno de España, 2018). A través este se lanzó la campaña #CoNprueba, basada en trasladar información veraz y accesible a la población para tomar

decisiones informadas y responsables acerca de las terapias sin o con escasa base científica.

Esta medida se realizó en colaboración con la Red Española de Agencias de Evaluación de Tecnologías y Prestaciones del Sistema Nacional de Salud (REDETS), quienes identificaron 139 terapias dudosas, de las cuales 73 no presentaban ningún estudio científico acerca de su eficacia o seguridad, por lo cual pasaron directamente a considerarse pseudoterapias (Figura 2).

Figura 2. Técnicas consideradas psudoterapias por el Ministerio de sanidad. Fuente: https://www.sanidad.gob.es/gabinete/notasPrensa.do

Para las 66 terapias restantes, entre las cuales aparecen la gran mayoría de las terapias complementarias y alternativas más utilizadas, se procedió a la revisión individual de cada una de ellas, generando los consecuentes informes y publicándolos en la web www.coNprueba.es para que puedan ser leídos por el público nacional. Hasta el momento, y relacionado con la Fisioterapia, en la web aparecen informes acerca de técnicas como el pilates, la terapia floral, el yoga, la meditación, la musicoterapia, el masaje estructural profundo, la acupuntura, la magnetoterapia, y el masaje tailandés (Figura 3).

Figura 3. Técnicas consideradas bajo evaluación por el Ministerio de sanidad. Fuente: https://www.sanidad.gob.es/gabinete/notasPrensa.do

Sin embargo, todavía hay múltiples terapias en evaluación relacionadas al ámbito de la Fisioterapia como la osteopatía, la quiropraxia, la reflexología podal o reflexoterapia, o el reiki.

1.2.3. La Osteopatía

Desde el primer artículo publicado en 1945, los estudios en el ámbito de la osteopatía han crecido exponencialmente hasta la actualidad, publicando actualmente más de 20.000 artículos al año y alcanzando su pico en 2021 con más de 24.000 artículos publicados (Figura 4). El primer ensayo clínico encontrado data de 1963. Uno de los principales problemas a la hora de valorar los estudios y la calidad de los mismos en el ámbito de la osteopatía es que menos de 200 son ensayos clínicos, el resto son estudios piloto, protocolos, series de casos y casos clínicos o encuestas de caracterización de la osteopatía en los diferentes países del mundo, o monográficos de personajes ilustres del ámbito de la osteopatía. Además, la mayoría de estos estudios están publicados en revistas indexadas dentro de la categoría de *Integrative and Complementary Medicine* en revistas como la *International Journal of Osteopathic Medicine*, *Journal of Osteopathy*, o *European Journal of Osteopathic Research*. Esto a primera vista puede hacer sospechar de un riesgo de sesgo de publicación.

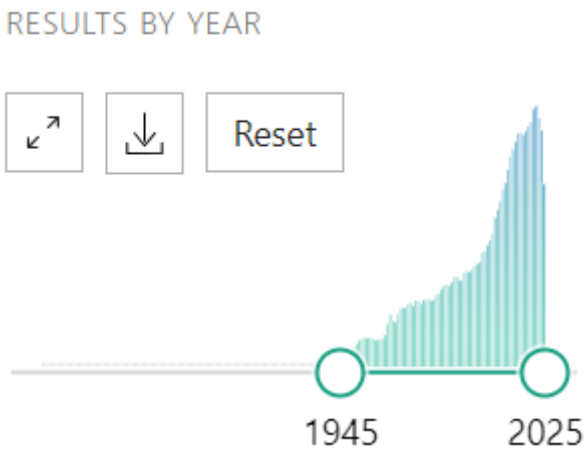

Figura 4. Evolución de los estudios de osteopatía desde el primer artículo publicado en la base de datos Medline. Fuente: https://pubmed.ncbi.nlm.nih.gov/?term=%28osteopath%5BMeSH%5D+OR+osteopathic+medicine%5BMeSH%5D+OR+osteopathic+manipulation%5BMeSH%5D+OR+osteopathic+manipulative+treatment%5BMeSH%5D%29+NOT+pilot+NOT+feasibility+NOT+protocol+NOT+feasible+NOT+quasi-experime

1.2.3.1. Historia de la Osteopatía

La osteopatía, proveniente de las palabras griegas *osteon* (referente al hueso) y *pathos (*referente a sufrimiento), fue desarrollada por Andrew Taylor Still (1828-1917) como una respuesta a lo que consideraba dañino de la medicina de aquella época tras haber sufrido situaciones traumáticas con esta como la muerte de uno de sus hijos (Hamonet, 2003).

Se describe en la literatura osteopática que A.T. Still era un médico y cirujano, sin embargo, esto está en debate. Los acérrimos a la profesión defienden su titulación como médico, pero los historiadores afirman que no pudo haber estudiado medicina de ninguna manera. Esto es así, ya que en los años de juventud de A.T. Still, en Estados Unidos, todavía se estaban creando las primeras escuelas de medicina. Los médicos norteamericanos se formaban principalmente mediante un aprendizaje, que a veces duraba sólo unos meses, durante el cual otros médicos les enseñaban los rudimentarios procedimientos de su profesión. Sin embargo, en 1893, A.T. Still obtuvo la autorización (registrada bajo el N° 71) para ejercer como “Médico” y “Cirujano” en el condado de Macon, Missouri (EE. UU). A.T. Still también practicaba otros procedimientos como el *bone-setting*, la frenología (referente a que la forma y posición del cráneo define aspectos psicológicos) y el

mesmerismo (curación magnética). La primera escuela independiente de osteopatía fue fundada en 1892 (Hamonet, 2003).

Esta corriente paralela a la medicina tradicional parece haber tenido repercusión en la actualidad haciendo que muchos osteópatas estén fuera de la evidencia científica actual. En su propia autobiografía, A.T. Still describe varios casos pacientes sobre los cuales basó la fundación de la osteopatía como son (Hamonet, 2003):

- **Su primer paciente**: el primer éxito documentado utilizando principios osteopáticos fue el tratamiento de un niño que sufría de disentería. Alrededor de 1874, A.T. Still trató a este niño, que había estado gravemente enfermo de la enfermedad y no respondía a los tratamientos convencionales. Mediante la manipulación de la columna vertebral y el abdomen, A.T. Still pretendía restablecer las funciones naturales del cuerpo. El niño se recuperó y este caso se convirtió en un momento clave en el desarrollo de sus técnicas osteopáticas.

- **Él mismo tras recibir un golpe en la cabeza con una pelota**: se tumbó en el suelo, se colocó una cuerda envuelta en una tela bajo el cuello a 10-15 cm del suelo y utilizó el aparato como almohada oscilante. Su dolor de cabeza desapareció, así como el dolor de estómago que lo acompañaba, y pudo dormir. Según su autobiografía siguió utilizando este método durante 20 años siempre que sentía la necesidad.

A.T. Still buscó explicaciones lógicas y mecanicistas a estos efectos. En el caso de la almohada afirmó que el dispositivo actuaba sobre los grandes nervios occipitales, armonizando así los flujos venosos y arteriales. Para explicar el resto de los casos describió "*un trastorno mecánico en el cuerpo causa todas las dolencias que se observan en los humanos y puede corregirse solo mediante osteopatía*" (Hamonet, 2003). De este modo, A.T. Still creía que desequilibrios mecánicos, principalmente en la columna, podría causar la obstrucción de flujos y originar todo tipo de enfermedades. De este razonamiento nació "la ley de la arteria" y A.T. Still defendió que "*la regla de la arteria debe ser universal y sin obstrucciones, o la enfermedad será el resultado*" (Hamonet, 2003). Por supuesto, la manipulación osteopática de la columna vertebral era la única herramienta que podía corregir estos desequilibrios mecánicos. De este modo, el osteópata era realmente un "médico práctico".

1.2.3.2. Fundamentos de la osteopatía

La osteopatía utiliza un enfoque holístico en el estado del paciente, entendiéndolo como una unidad funcional dinámica en la cual todas las partes están interrelacionadas y posee una serie de mecanismos autorregulatorios y de autocuración. En este sentido habla de la relación entre el cuerpo, la mente y el espíritu en la creación y curación de patologías. Este marco filosófico dentro del entendimiento del cuerpo es lo que realmente lo hace diferente a otra serie de métodos de terapia manual.

Los principios fundamentales de la osteopatía en su creación fueron los siguientes:

- El cuerpo es una unidad
- El cuerpo tiene mecanismos de autorregulación natural
- La estructura y la función están interrelacionados a todos los niveles
- El tratamiento debe ser basado en el entendimiento del cuerpo como una unidad, mecanismos de autorregulación y la interrelación entre la estructura y la función.

Estos principios han evolucionado a lo largo del tiempo siendo su última actualización en 2002 por el *Kirksville College of Osteopathic Medicine* (Fryer, 2011).

- La persona es el producto de una interacción dinámica entre cuerpo, mente y espíritu.
- Esta interacción dinámica incluye la capacidad inherente del individuo para mantener la salud y recuperarse de la enfermedad.
- Diversas fuerzas, tanto intrínsecas como extrínsecas, pueden amenazar esta capacidad inherente y contribuir a la aparición de enfermedades.
- El sistema musculoesquelético influye significativamente en la capacidad del individuo para restaurar esa capacidad inherente de resistir procesos patológicos.

1.2.3.3. Principales técnicas de tratamiento osteopáticas

La osteopatía por definición se basa en técnicas manuales para el diagnóstico y el tratamiento. El diagnóstico se caracteriza por ser realizado exclusivamente a través de la palpación manual con el objetivo de localizar las llamadas “disfunciones somáticas”. Estas se definen como "f*uncionamiento deteriorado o alterado de los componentes relacionados del sistema estructural del cuerpo: estructuras esqueléticas, articulares y*

miofasciales, y sus componentes vasculares, linfáticos y neurales relacionados, y/o sensibilidad" (American Association of Colleges of Osteopathic Medicine (AACOM), 2017). Los aspectos posicionales y de movimiento de la disfunción somática se describen generalmente mediante:

1. La posición de una parte del cuerpo determinada por palpación y referida a su estructura adyacente definida.
2. Las direcciones en las que el movimiento es más libre.
3. Las direcciones en las que el movimiento está restringido.

Las disfunciones somáticas se evalúan o identifican por:

1. Existencia de una asimetría posicional
2. Presencia de un rango de movimiento restringido
3. Palpación de anormalidades en la textura de los tejidos.

De este modo, las disfunciones somáticas solo son tratables mediante tratamiento manipulativo osteopático. Estas técnicas a su vez pueden estar dirigidas al sistema óseo, articular, a las estructuras miofasciales e incluso a elementos vasculares, neurales y linfáticos relacionados para restaurar la función fisiológica y/o apoyar la homeostasis que se ha visto alterada por estas disfunciones somáticas (Chila, 2010; Richard, 2014).

Comúnmente, la osteopatía se subdivide en tres ramas, como son la estructural, la visceral y la craneal.

- **Osteopatía estructural**

La osteopatía estructural se basa en la asunción de que las desviaciones de la estructura anatómica del cuerpo están asociadas a disfunciones somáticas que causan dolor y enfermedades tanto musculoesqueléticas como no musculoesqueléticas, y cuyo tratamiento mediante terapia manual osteopática puede solucionar (Chila, 2010; Richard, 2014).

- **Osteopatía visceral**

La osteopatía visceral fue desarrollada principalmente por Jean Pierre Barral y Pierre Mercier en la década de 1980. El modelo biológico de la osteopatía visceral se basa en que la falta de movimiento o la malposición de la víscera crea patrones de tensión anormales e irritación crónica causando problemas funcionales y estructurales en todo el cuerpo,

pudiendo resultar en problemas tanto neuromusculoesqueléticos como viscerales (Barral & Mercier, 2004).

Entre los más llamativos ejemplos se pueden encontrar la palpación del corazón, la palpación de la memoria sistólica impresa en la fascia pericárdica, la relación entre la fascia pericárdica y la pelvis, o los problemas en la pelvis y las infecciones del tracto urinario. También se ha descrito una relación entre la estructura visceral y la psicología considerando que las vísceras tienen memoria. En el libro de Jean Pierre Barral se describen algunos ejemplos como: "*el hígado memoriza todos los elementos que construyen nuestra identidad*", la vesícula biliar "*normalmente se preocupa por cosas sin importancia*" o el páncreas "*reacción* a muertes que no han sido aceptadas" (Hidalgo et al., 2024).

Su tratamiento se basa en que las movilizaciones manuales conocidas como manipulaciones viscerales restauran la movilidad, eliminan las adherencias, disminuyen la tensión fascial, y mejoran la función de la víscera normalizando el estado de excitabilidad de las neuronas ¡aferentes del sistema nervioso central (Barral & Mercier, 2004).

- **Osteopatía craneal**

La osteopatía craneal o craneosacra fue creada por William Sutherland en 1962. Este proponía que las suturas del cráneo se parecían a las branquias de un pez y, siguiendo este pretexto según el cual la respiración mueve las branquias, asumió que existía un movimiento respiratorio primario a través del cual se podían mover las suturas craneales. Cuando este movimiento se veía alterado podía desembocar en todo tipo de problemas de salud (Ernst, 2012; World Health Organization, 2010). El mecanismo respiratorio primario como concepto central de la osteopatía craneal presenta cinco elementos clave:

- Fluctuación inherente del líquido cefalorraquídeo. El movimiento del líquido cefalorraquídeo puede ser percibido por los osteópatas.
- Movilidad del sistema nervioso central. Provoca la fluctuación del líquido cefalorraquídeo.
- Movilidad de las membranas intracraneales y espinales. Las membranas que rodean el cerebro y la médula espinal también presentan movimientos.
- Movilidad de los huesos craneales. Los huesos del cráneo se mueven.

- Movimientos involuntarios del sacro entre los huesos ilíacos. El sacro también participa en el movimiento respiratorio primario por su conexión con el cráneo a través de las membranas durales.
- El poder o aliento de la vida. Concepto abstracto en el que se postula que una fuerza vital impulsa estos ritmos y movimientos.

Según este concepto, el mecanismo respiratorio primario son movimientos rítmicos intrínsecos del cerebro que causan fluctuaciones el en líquido cefalorraquídeo y cambios específicos en las membras durales, huesos del cráneo y sacro, que pueden ser palpados manualmente, y que cuando se ve alterado se provocan diversos tipos de problemas de salud. Por lo que el diagnóstico de estas alteraciones se realiza mediante la palpación manual y su tratamiento se basa en el uso de movilizaciones, manipulaciones craneales o terapia craneosacral con el objetivo de restaurar el equilibrio del sistema.

1.2.3.4. Plausibilidad biológica de la osteopatía

Considerando el rumbo que ha tomado la evidencia científica actual en el campo de la Fisioterapia, los principios expuestos de la osteopatía, así como los fundamentos de su aplicación tanto en forma de diagnóstico como de tratamiento dejan entrever serios problemas en el caso de la plausibilidad biológica de sus bases. Entre los principales problemas encontramos:

- **La naturaleza biomecánica**:

La osteopatía defiende que, a través de esta, el dolor, la patología y la enfermedad se deben a problemas mecánicos objetivables en la estructura, función o fisiología. Sin embargo, la evidencia actual se ha demostrado contraria a esta creencia, exponiendo que no siempre existe una relación entre el dolor y los cambios estructurales en patologías musculoesqueléticas. Incluso que personas asintomáticas presentan asimetrías, diferentes posiciones, y variaciones anatómicas (Phillips, 2022; Thomson & MacMillan, 2023; Thomson & Martini, 2024).

Uno de los principales problemas acerca de la naturaleza biomecánica es que, desde el punto de vista de la osteopatía, se pueden tratar otros trastornos no musculoesqueléticos como la otitis, las anginas, los trastornos de déficit de atención, la depresión, el retraso en el desarrollo del habla, el cólico del lactante, la parálisis cerebral etc… debido a que las

disfunciones somáticas musculoesqueléticas también pueden causar enfermedades musculoesqueléticas. A día de hoy no existe ninguna evidencia de esta relación.

- **El posibilismo anatómico:**

El posibilismo anatómico prioriza el conocimiento anatómico para construir narrativas y justificar enfoques terapéuticos que van más allá de la anatomía y fisiología basada en la evidencia para guiar la práctica clínica. En este sentido, se puede observar la existencia de un anatomismo holístico que se refiere al diseño de conexiones entre regiones anatómicas, sistemas y tejidos que son imaginadas o exageradas con el único objetivo de justificar la aplicación de una terapia (Chila, 2010; Hidalgo et al., 2024). El mejor ejemplo de esto sigue siendo la relación entre la disfunción musculoesquelética y la patología no musculoesquelética, o las interconexiones fasciales que unen todo el cuerpo pudiendo cambiar la estructura de un músculo periférico a través del tratamiento suboccipital, por ejemplo (Jiang et al., 2023).

La osteopatía defiende que todo en el cuerpo está conectado y por lo tanto todo importa, entendiendo el cuerpo humano como una completa máquina y justificando así enfoques osteopáticos holísticos. Sin embargo, gran parte de este estructuralismo anatómico es implausible.

- **Monointervencionismo:**

A pesar de que la osteopatía se define y se defiende como un método holístico, toda ella se basa en el diagnóstico manual de las denominadas disfunciones somáticas y en el tratamiento mediante sus propias técnicas manuales, dejando en entredicho el concepto de holístico (Álvarez-Bustins et al., 2018; Ellwood & Carnes, 2021; Plunkett et al., 2022; Wagner et al., 2023).

De hecho, esto ha propiciado la división de la osteopatía en sus tres principales ramas como son la osteopatía estructural, osteopatía visceral y osteopatía craneal. De este modo, no solo no se aplica la base holística, sino que se genera una simplificación de las patologías en tres categorías que pueden ser diagnósticas y tratadas manualmente, ignorando el modelo biopsicosocial actual de actuación.

- **Las tomas de decisiones:**

Los métodos de actuación actuales defienden que se debe tener en consideración las preferencias de los pacientes. Sin embargo, estas no son utilizadas por los osteópatas, ya

que al regirse por sus propios principios y su propia plausibilidad biológica deben de utilizar sus propias tomas de decisiones sin tener en cuenta las preferencias y disposiciones del paciente ante el tratamiento, ya que no sigue los conceptos de la FBE (Browne et al., 2019; Thomson et al., 2014).

- **Mecanismos implausibles:**

La osteopatía está repleta de teorías complicadas, enrevesadas y muchas veces infalsificables basadas en las interpretaciones, experiencias y observaciones de un reducido número de individuos. Diversos autores han señalado la incoherencia de estos modelos que sobre simplifican la situación para que se adapte a la aplicación de técnicas manuales y que, por lo tanto, no tienen plausibilidad biológica ni apoyo empírico y que están más cerca de la pseudociencia que de la práctica basada en la evidencia (Hartman, 2009; Thomson & MacMillan, 2023). Entre los ejemplos a destacar está el uso de técnicas craneales o manipulativas de columna en recién nacidos, ya que en el proceso de nacimiento se pueden ocasionar presiones extremas en la estructura craneal del bebé o que una mala posición en el útero puede provocar disfunción espinal (Dobson et al., 2014). Otros ejemplos son las torsiones del sacro, las disfunciones de la primera costilla, la alteración de las suturas craneales o la presencia de órganos rotados o desplazados como diagnósticos principales.

En este sentido, queda expuesto que la osteopatía y sus tres principales vertientes no cuentan con el respaldo actual de la evidencia científica en términos de plausibilidad biológica, por lo que según la clasificación de Pigliucci (Pigliucci & Boudry, 2013), la osteopatía solo podría aspirar a ciencia blanda o pseudociencia. En este sentido se corrobora su buen posicionamiento según el Ministerio de Educación y Ciencia como posible pseudoterapia. El paso que nos queda por dar para clasificarla finalmente como pseudoterapia o como ciencia blanda es evaluar su efectividad clínica en las diferentes patologías musculoesqueléticas y no musculoesqueléticas.

1.3. JUSTIFICACIÓN DEL ESTUDIO

Actualmente, la profesión de la Fisioterapia se rige de manera general por la FBE y, en particular, por la práctica clínica basada en la evidencia. Esta aplicación clínica requiere en primer lugar, de un esfuerzo por parte de los profesionales de conocer de manera previa lo que hay publicado; y, en segundo lugar, de saber utilizar esta información de forma lógica en la toma de decisiones reemplazando, modificando, o enriqueciendo los métodos, técnicas, procedimientos, planes, protocolos o programas.

Para el desarrollo adecuado de una práctica clínica efectiva es necesario localizar siempre los estudios que respondan con la mayor certeza a las preguntas clínicas que se planteen. En este sentido, se recomienda siempre la búsqueda de revisiones sistemáticas con y sin meta-análisis así como los ensayos clínicos originales cuando no exista una guía clínica que aborde el problema.

Sin embargo, se debe comprender que la Fisioterapia es una profesión de corto tiempo de evolución, lo que dificulta la respuesta concisa de múltiples preguntas y, a su vez, la aparición de nuevas intervenciones que podrían llevar a nuevas respuestas. Estas nuevas terapias se engloban bajo las denominadas terapias complementarias y alternativas, lo cual quiere decir que no han sido sometidas a estudios científicos rigurosamente diseñados y ejecutados y que sus preguntas esenciales acerca de la verificación y falsación aún deben de responderse.

En función de cómo se respondan a estas preguntas, según la clasificación de Puglicci las podremos denominar como: 1) ciencia establecida, referente a que ha mostrado una plausibilidad biológica y efectividad clínica (por lo que pasaría a formar parte de la FBE); 2) Protociencia: ha mostrado plausibilidad biológica, pero efectividad clínica limitada; 3) ciencia blanda: muestra efectividad clínica pero no plausibilidad biológica; y 4) no ha conseguido demostrar ni plausibilidad biológica ni efectividad clínica.

Dentro del ámbito de Fisioterapia, la osteopatía es uno de los métodos que está en debate. Esta se basa en un enfoque holístico en el estado del paciente, exponiendo que todas las partes están interrelacionadas y posee una serie de mecanismos autorregulatorios y de autocuración. Se basa en la relación entre el cuerpo, la mente y el espíritu en la creación y curación de patologías. Sus cuatro principios fundamentales fueron inicialmente: 1) el cuerpo es una unidad; 2) el cuerpo tiene mecanismos de autorregulación natural; 3) la estructura y la función están interrelacionados a todos los niveles; y 4) el tratamiento debe

ser basado en el entendimiento del cuerpo como una unidad, mecanismos de autorregulación y la interrelación entre la estructura y la función.

Sin embargo, el problema que ha mostrado al relacionarse con la FBE es que sus fundamentos carecen de una plausibilidad biológica por exponer una naturaleza puramente biomecánica, basada en el denominado posibilismo anatómico y mecanismos implausibles para justificar un monointervencionismo basado en técnicas manuales y sobre las cuales la toma de decisión es principalmente del terapeuta sin atender a las condiciones del paciente.

A partir de esto, surge la necesidad de investigar la efectividad clínica de la osteopatía, para conocer si presenta un soporte empírico y puede clasificarse como una ciencia blanda, o si, por el contrario, no existe tal evidencia clínica y debe entrar en la denominación de pseudoterapia.

HIPÓTESIS Y OBJETIVOS

2 HIPÓTESIS Y OBJETIVOS

2.1 HIPÓTESIS

2.1.1 Hipótesis conceptual

Las técnicas osteopáticas estructurales, viscerales y/o craneales no producen efectos clínicos superiores a un placebo, un control basado en una terapia conservadora convencional, o la ausencia de tratamiento en patologías musculoesqueléticas y no-musculoesqueléticas.

2.1.2 Hipótesis operacional

1. Las técnicas osteopáticas estructurares no producen efectos clínicos superiores a un placebo en patologías musculoesqueléticas.

2. Las técnicas osteopáticas basadas en manipulación visceral no producen efectos clínicos superiores a un placebo o un control basado en terapias conservadoras no farmacológicas en patologías musculoesqueléticas y no musculoesqueléticas.

3. Las técnicas osteopáticas craneosacras no producen efectos clínicos superiores a un placebo, un control basado en terapias conservadoras no farmacológicas, o a la ausencia de tratamiento en patologías musculoesqueléticas y no musculoesqueléticas.

2.2 OBJETIVOS

2.2.1 Objetivo general

Revisar crítica y sistemáticamente la evidencia de manera narrativa y cuantitativa acerca de la efectividad clínica de la osteopatía estructural, visceral y/o craneal en todas las patologías musculoesqueléticas y no musculoesqueléticas estudiadas.

2.2.2 Objetivos específicos

1. Revisar crítica y sistemáticamente la evidencia de manera narrativa y cuantitativa acerca de la efectividad clínica de la osteopatía estructural en todas las patologías musculoesqueléticas estudiadas.

2. Revisar crítica y sistemáticamente la evidencia de manera narrativa y cuantitativa acerca de la efectividad clínica de la osteopatía visceral en todas las patologías musculoesqueléticas y no musculoesqueléticas estudiadas.

3. Revisar crítica y sistemáticamente la evidencia de manera narrativa y cuantitativa acerca de la efectividad clínica de la osteopatía craneal en todas las patologías musculoesqueléticas y no musculoesqueléticas estudiadas.

4. Describir los efectos específicos, los factores contextuales y los factores no específicos que pueden verse relacionados con la práctica osteopática.

METODOLOGÍA

3 METODOLOGÍA

Los objetivos mencionados en el apartado anterior han sido alcanzados mediante la realización de cuatro investigaciones publicadas en cuatro artículos científicos diferentes que han sido recopilados en la presente tesis doctoral en formato de compendio de publicaciones.

Los tres primeros objetivos acerca de revisar crítica y sistemáticamente la evidencia de manera narrativa y cuantitativa acerca de la efectividad clínica de la osteopatía estructural, visceral y craneal se ha conseguido con la realización de tres revisiones sistemáticas con meta-análisis siguiendo los criterios PRISMA de estudios que han aplicado técnicas osteopáticas basadas en los tejidos diana anteriormente descritos en comparación con intervenciones placebo, controles basados en terapias conservadoras no farmacológicas, o la ausencia de intervención en diversas patologías musculoesqueléticas y no musculoesqueléticas. Con estas revisiones hemos conseguido recopilar todos los ECA que hay en la literatura acerca de la osteopatía (acorde a las bases de datos de búsqueda utilizadas), y sintetizar y cuantificar los efectos clínicos que presentan. Las publicaciones que se presentan para este apartado son:

- Ceballos-Laita L, Jiménez-Del-Barrio S, Carrasco-Uribarren A, Medrano-de-la-Fuente R, Robles-Pérez R, Ernst E. Is Osteopathic Manipulative Treatment Clinically Superior to Sham or Placebo for Patients with Neck or Low-Back Pain? A Systematic Review with Meta-Analysis. Diseases. 2024 Nov 8;12(11):287. doi: 10.3390/diseases12110287. PMID: 39589961; PMCID: PMC11593019.

- Ceballos-Laita L, Ernst E, Carrasco-Uribarren A, Esteban-Tarcaya G, Mamud-Meroni L, Jiménez-Del-Barrio S. Is visceral osteopathy therapy effective? A systematic review and meta-analysis. International Journal of Osteopathic Medicine. 2024 Jul 54:100729. doi: 10.1016/j.ijosm.2024.100729

- Ceballos-Laita L, Ernst E, Carrasco-Uribarren A, Cabanillas-Barea S, Esteban-Pérez J, Jiménez-Del-Barrio S. Is Craniosacral Therapy Effective? A Systematic Review and Meta-Analysis. Healthcare (Basel). 2024 Mar 18;12(6):679. doi: 10.3390/healthcare12060679. PMID: 38540643; PMCID: PMC10970181.

Para alcanzar el cuarto objetivo acerca de "describir los efectos específicos, los factores contextuales y los factores no específicos que pueden verse relacionados con la práctica

osteopática” se ha realizado una revisión narrativa de todos los estudios encontrados en los últimos 25 años acerca de la plausibilidad bilógica, mecanismos de acción o efectividad clínica de las terapias complementarias y alternativas en general y de la osteopatía en particular. Con esta revisión hemos conseguido dar una visión de todos los factores que intervienen en la práctica clínica de terapias que no cuentan con el aval de una plausibilidad biológica, pero que sin embargo muestran ciertos aspectos clínicos positivos. La publicación que se presenta para este apartado es:

- Mamud-Meroni L, Tarcaya GE, Carrasco-Uribarren A, Rossettini G, Flores-Cortes M, Ceballos-Laita L. "The Dark Side of Musculoskeletal Care": Why Do Ineffective Techniques Seem to Work? A Comprehensive Review of Complementary and Alternative Therapies. Biomedicines. 2025 Feb 6;13(2):392. doi: 10.3390/biomedicines13020392. PMID: 40002804; PMCID: PMC11853516.

A continuación, se presentan los estudios publicados en relación a los objetivos planteados.

PUBLICACIONES

4 PUBLICACIONES INCLUIDAS

4.1. Publicación nº1

Título: **Is Osteopathic Manipulative Treatment Clinically Superior to Sham or Placebo for Patients with Neck or Low-Back Pain? A Systematic Review with Meta-Analysis**

Autores: **Luis Ceballos-Laita, Sandra Jiménez-del-Barrio, Andoni Carrasco-Uribarren, Ricardo Medrano-de-la-Fuente,Román Robles-Pérez y Edzard Ernst**

Revista: Diseases

Factor de impacto: 2.9

Cuartil: 91/189

DOI:10.3390/diseases12110287

4.2. Publicación nº2

Título: **Is visceral osteopathy therapy effective? A systematic review and meta-analysis**

Autores: **Luis Ceballos-Laita, Edzard Ernst, Andoni Carrasco-Uribarren, German Esteban-Tarcaya, Lucas Mamud-Meroni, Sandra Jimenez-del-Barrio**

Revista: International Journal of Osteopathic Medicine

Factor de impacto:1.1

Cuartil: 163/329

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4.3. Publicación nº3

Título: **Is Craniosacral Therapy Effective? A Systematic Review and Meta-Analysis**

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4.4. Publicación nº4

Título: **“The Dark Side of Musculoskeletal Care”: Why Do Ineffective Techniques Seem to Work? A Comprehensive Review of Complementary and Alternative Therapies**

Autores: **Lucas Mamud-Meroni, Germán E. Tarcaya, Andoni Carrasco-Uribarren, Giacomo Rossettini, Mar Flores-Cortes and Luis Ceballos-Laita**

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Systematic Review

Is Osteopathic Manipulative Treatment Clinically Superior to Sham or Placebo for Patients with Neck or Low-Back Pain? A Systematic Review with Meta-Analysis

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Abstract: Objectives: The aim of this systematic review and meta-analysis was to compare whether osteopathic manipulative treatment (OMT) for somatic dysfunctions was more effective than sham or placebo interventions in improving pain intensity, disability, and quality of life for patients with neck pain (NP) or low-back pain (LBP). **Methods**: A systematic review and meta-analysis was carried out. Searches were conducted in PubMed, Physiotherapy Evidence Database, Cochrane Library, and Web of Science from inception to September 2024. Studies applying a pragmatic intervention based on the diagnosis of somatic dysfunctions in patients with NP or LBP were included. The methodological quality was assessed with the PEDro scale. The quantitative synthesis was performed using random-effect meta-analysis calculating the standardized mean difference (SMD) with RevMan 5.4. The certainty of evidence was evaluated using GRADEPro. **Results**: Nine studies were included in the qualitative synthesis, and most of them showed no superior effect of OMTs compared to sham or placebo in any clinical outcome. The quantitative synthesis reported no statistically significant differences for pain intensity (SMD = −0.15; −0.38, 0.08; seven studies; 1173 patients) or disability (SMD = −0.09; −0.25, 0.08; six studies; 1153 patients). The certainty of evidence was downgraded to moderate, low, or very low. **Conclusions**: The findings of this study reveal that OMT is not superior to sham or placebo for improving pain, disability, and quality of life in patients with NP or LBP.

Keywords: osteopathy; osteopathic manipulative treatment; neck pain; low-back pain

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1. Introduction

Neck pain (NP) and low-back pain (LBP) are the most common causes of pain and disability in adult populations [1,2]. They affect more than 80% of people at least once in their lifetime, and their prevalence is rising in all age groups [3–6], leading to an increased demand for healthcare consultations and considerable financial burden for societies across the globe. Many patients suffering NP or LBP turn to complementary and alternative therapies, such as osteopathy [7–9].

Osteopathy is a holistic approach that focuses on the manual manipulation of the musculoskeletal system to restore physiological function and support homeostasis, which may be disrupted by somatic dysfunctions. This practice, commonly known as Osteopathic Manipulative Treatment (OMT), is claimed to promote overall wellness without reliance on pharmaceuticals or invasive procedures [10].

OMT uses manual techniques either for the diagnosis and for treatment of so-called somatic dysfunctions, defined as the "impaired or altered function of components of the

somatic system, including skeletal, arthrodial, and myofascial structures, as well as related vascular, lymphatic, and neural elements, and it is characterized by positional asymmetry, restricted range of motion, tissue texture abnormalities, and/or tenderness" [11]. The diagnosis of somatic dysfunctions relies on the manual palpation of tissues to identify these specific characteristics. Osteopathic interventions incorporate a wide range of manual techniques to treat somatic dysfunctions, including visceral manipulation, craniosacral techniques, high-velocity low-amplitude (HVLA) adjustments, articulatory techniques, soft-tissue stretching, myofascial release, and muscle energy techniques, among others. Osteopathic interventions are applied to the entire body, regardless of the symptomatic area, either independently or in combination with other treatments.

Several systematic reviews with meta-analyses found clinical benefits from a combination of osteopathic techniques in patients with NP and LBP [12–15]. However, these reviews have methodological flaws, such as including congress abstracts, pilot studies that do not aim to evaluate clinical effectiveness, and unpublished materials from osteopathic institutions as relevant studies. These studies also combine quantitative results from studies using cranial or visceral interventions in isolation with those using pragmatic interventions, and treat different comparators (such as exercise, placebo techniques or waiting lists) as if they were equivalent. Recent systematic reviews and meta-analyses have evaluated the clinical effectiveness of craniosacral interventions and visceral manipulations in isolation either in musculoskeletal or non-musculoskeletal disorders, and both reviews concluded that cranial and visceral osteopathy is not supported by sound evidence [16,17].

Therefore, the aim of this systematic review and meta-analysis is to determine whether OMTs for so-called somatic dysfunctions are more effective than sham or placebo interventions in improving clinical outcomes for patients with NP or LBP.

2. Materials and Methods

2.1. Study Design

This systematic review and meta-analysis was carried out following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement and the Cochrane recommendations for systematic reviews with meta-analyses [18]. The study protocol was pre-registered in PROSPERO under the unique identification number (CRD42024595500).

2.2. Search Strategy

Searches were conducted in PubMed (MEDLINE), the Physiotherapy Evidence Database (PEDro), the Cochrane Library, and Web of Science (WoS) from inception to September 2024. Medical Subject Headings (MeSH) terms and free-text keywords, including "osteopathic manipulation", "osteopathic medicine", "osteopathic treatment", "osteopathic intervention", "osteopathic manipulative treatment", "neck pain", and "low-back pain", were used in the search strategy. The specific search strategy for each database is detailed in Appendix A. Additionally, the reference lists of the included studies and relevant previous systematic reviews were manually searched.

2.3. Eligibility Criteria

The inclusion criteria were developed following the PICOS method:

- Population: Patients with NP or LBP as diagnosed clinically.
- Intervention: Holistic approach of OMT based on the diagnosis of the somatic dysfunctions. According to the benchmarks for training in osteopathy, OMT includes articular, myofascial, cranial, and visceral techniques [10].
- Comparison: Sham, placebo, or simulated techniques.
- Outcomes: Pain intensity, disability and/or quality of life.
- Study design: Randomized clinical trials.

Studies were excluded if they met the following criteria: included healthy participants or patients with non-musculoskeletal conditions, applied osteopathic techniques in isolation or did not apply a pragmatic OMT intervention based on the diagnosis of somatic dysfunctions, reported outcome variables not related to the clinical status of the patients, or the outcome variables were not registered using validated instruments.

2.4. Study Selection

The reference lists obtained from each database were exported to Mendeley to eliminate duplicates. Two authors (LC and SJ) independently assessed the titles and abstracts of each study to determine their potential eligibility. Full-text reviews were conducted for the studies that met the inclusion criteria after the title and abstract screening. In the case of discrepancies, a third reviewer was consulted to resolve them (RM).

Data Extraction

Data extraction was carried out independently by two reviewers (LC and SJ) using a predefined sheet based on the Cochrane Collaboration guidelines. The extracted data included population characteristics (mean age, diagnosis), details of the interventions (techniques applied, session duration, number of sessions per week, and total sessions), outcome variables, and results.

2.5. Methodological Quality Assessment

The methodological quality of the included studies was evaluated by two independent reviewers (LC and SJ) using the PEDro scale, which is based on an 11-item checklist developed from a Delphi consensus [19–21]. The PEDro scale assesses the methodological rigor of clinical trials by evaluating key aspects such as randomization, allocation concealment, blinding, and statistical reporting. A score of 0–3 was deemed "poor" methodological quality, scores between 4 and 5 were classified as "fair", scores from 6 to 8 were classified as good, and scores of 9 or above were classified as "excellent". The first item of the PEDro scale, which assesses the specification of eligibility criteria and pertains to external validity, was not included in the total score calculation. The remaining 10 items focus on internal validity and interpretability [22].

2.6. Data Synthesis and Analysis

A qualitative synthesis of the results was conducted, and whenever it was possible, a quantitative synthesis (meta-analysis) was carried out using the RevMan 5.4 software.

Data were combined for meta-analysis when at least two studies were sufficiently homogeneous. Mean differences (MD), standard deviations (SD), and sample sizes at each time point were extracted for each group. If MDs were not reported and could not be calculated, the post-intervention means were used. When none of the required data were provided in the articles, the authors were contacted via email to request the missing information.

Outcomes were analyzed by calculating the standardized mean difference (SMD) due to the use of different scales and questionnaires across the included studies, with 95% coefficient intervals (CIs). SMD values were interpreted as small (SMD between 0.2 and 0.5), medium (SMD between 0.5 and 0.8), or large (SMD ≥ 0.8) [23]. Statistical significance was set at p value < 0.05.

A Random-effect meta-analysis was conducted to account for the possibility that the studies were not estimating the same intervention effect [24]. Heterogeneity was assessed by considering the similarity of point estimates, the overlap of confidence intervals, the context of the results, and the I^2 statistic in the forest plots [25,26]. To evaluate publication bias and assess the influence of each study, we visually inspected the forest plot and performed sensitivity analyses by excluding individual studies. Funnel plots were not

reported, as no meta-analysis included at least 10 trials, which was the recommended threshold for such plots.

2.7. Certainty of Evidence Assessment

The certainty of evidence was evaluated using GRADE Evidence Profiles by independent reviewers. Evidence was categorized as "high", "moderate", "low", or "very low" to guide researchers and clinicians in interpreting the significance of the findings. This assessment was based on several key domains, including risk of bias, inconsistency, indirectness, imprecision, and other considerations.

The certainty of evidence was downgraded based on several factors: risk of bias (one level if ≥25% of participants were from studies classified as poor or fair methodological quality, and two levels if ≥50%), inconsistency of results (one or two levels depending on point estimate similarity, confidence interval overlap, I^2 statistic, and result context), indirectness of evidence (one level for differences in populations, interventions, or comparators), and imprecision (one or two levels for small sample sizes and wide confidence intervals) [25,26].

3. Results

Nine studies were eventually included in the qualitative synthesis and seven were included in the quantitative synthesis. The secondary analyses from the studies by Licciardone et al. [27–34] and Hansel et al. [35,36] were excluded to avoid data duplication, three studies were excluded for applying a single osteopathic technique without mentioning the holistic diagnosis of the patients [37–39], as well as another study that did not provide separate data for patients with NP and LBP [40] (Appendix B). The selection process is shown in the PRISMA flowchart diagram (Figure 1).

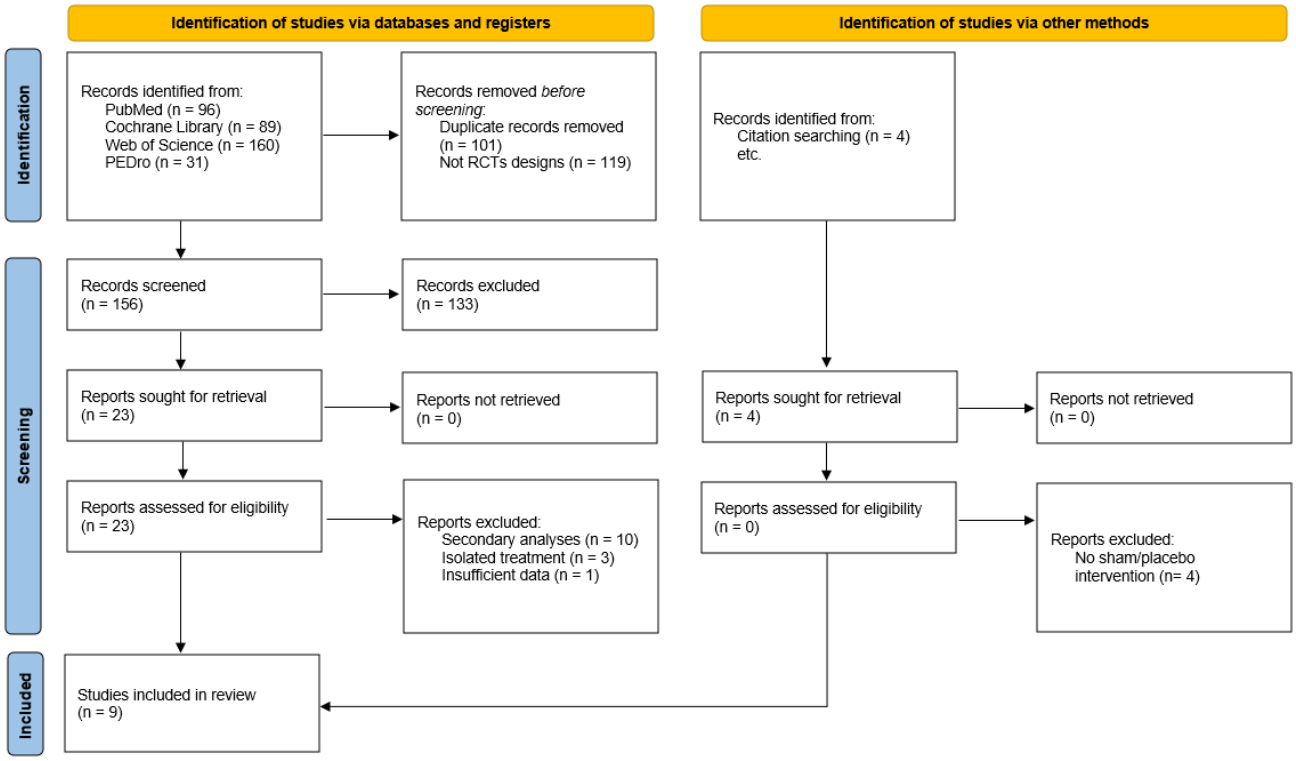

Figure 1. Flowchart diagram of the study.

3.1. Characteristics of the Included Studies

Nine RCTs were included, two comprising 26 patients with NP and seven comprising 1281 patients with LBP.

The studies included patients with non-specific NP [41,42], non-specific LBP [43–47], and pregnant women with LBP [48,49]. The sociodemographic and clinical characteristics of the participants of each study are shown in Table 1.

Table 1. Characteristics of the included studies and main results.

	Participants		**Intervention**		**Outcome (Tool)**	**Main Results**
Author (Year)	**Mean Age (SD)**	**Diagnosis**	**OMT Group**	**Sham/Placebo Group**		
Palmer et al., 2023 [42]	OMT:25.4 (2.4) Sham:25.0 (1.8)	NSNP	OMT (*n* = 10)	Light touch (*n* = 8)	Pain (VAS) Disability (NDI) QoL (SF-12) - Physical - Mental	ND ND ND ND
Schwerla et al., 2008 [41]	OMT:41.5 (6.1) Sham:44.8 (9.4)	NSNP	OMT (*n* = 21)	Placebo ultrasound (*n* = 16)	Pain (NRS) - Actual pain - Average pain - Worst pain QoL (SF-36) - Bodily pain	 ND ↑ ND ↑
Auger et al., 2021 [44]	OMT:25.9 (2.5) Sham:25.3 (1.6)	NSLBP	OMT (*n* = 10)	Light touch (*n* = 10)	Pain (VAS) Disability (ODI) QoL (SF-12) - Physical - Mental	ND ND ND ND
Nguyen et al., 2021 [42]	OMT:48.3 (11.9) Sham:47.5 (10.6)	NSLBP	OMT (*n* = 164)	Light touch (*n* = 159)	Pain (NRS) Disability (QBPDI) QoL (SF-12) - Physical - Mental	ND ↑ ND ND
Hensel et al., 2015 [49]	OMT:23.9 (4.1) Sham:24.1 (4.1)	Pregnant women with LBP	OMT (*n* = 136)	Placebo ultrasound (*n* = 133)	Pain (VAS) - Actual pain - Average pain - Best pain - Worst pain Disability (RMDQ)	 ND ND ND ND ND
Licciardone et al., 2013 [47]	OMT:41 (29–51) Sham:40 (29–50)	NSCLBP	OMT (*n* = 230)	Light touch (*n* = 225)	Pain (VAS) Disability (RMDQ) QoL (SF-36)	↑ ND ND
Licciardone et al., 2010 [48]	OMT:23.8 (5.5) Sham:23.7 (4.4)	Pregnant women with LBP	OMT (*n* = 48)	Placebo ultrasound (*n* = 47)	Pain (VAS) Disability (RMDQ)	ND ND
Licciardone et al., 2003 [46]	OMT:49 (12) Sham:52 (12)	NSCLBP	OMT (*n* = 32)	Light touch and sham OMT (*n* = 19)	Pain (VAS) Disability (RMDQ) QoL (SF-36)	ND ND ND
Gibson et al., 1985 [45]	OMT:34 (14) Sham:40 (14)	NSLBP	OMT (*n* = 35)	Placebo short-wave diathermy (*n* = 33)	Pain (VAS) - Daytime pain - Nocturnal pain	 ND ND

OMT: Osteopathic manipulative treatment; NSNP: non-specific neck pain; NSLBP; non-specific low-back pain; LBP: low-back pain; NSCLBP: non-specific chronic low-back pain; VAS: visual analog scale; NRS: numerical rating scale; NDI: neck disability index; ODI: oswestry disability index; QBPDI: Quebec back pain disability index; RMDQ: Roland Morris disability questionnaire; QoL:

quality of life; SF-12: short-form health survey; SF-36: short-form health survey; ND: no statistical differences; ↑: statistically significant differences in favor to the OMT group.

The interventions applied varied widely, but all were based on individual diagnoses of somatic dysfunctions. Each study pragmatically employed a range of OMTs, combining articular, myofascial, cranial, and/or visceral techniques. Regarding the frequency and duration of the interventions, the most common treatment schedule was one session every one to two weeks, with the intervention duration typically ranging from eight to twelve weeks. A detailed description of the interventions used in each study is provided in Table 2.

Table 2. Characteristics of the interventions.

	Intervention				
Author (Year)	**OMT Group**	**Sham/Placebo Group**	**Session Duration**	**Frequency**	**Total Number of Sessions (Weeks)**
Palmer et al., 2023 [42]	- Suboccipital release - Cervical contralateral traction - Upper thoracic spine unilateral soft tissue pressure - Thoracic inlet/outlet myofascial release - Atlanto–occipital and atlanto–axial, and C2-7 somatic dysfunction muscle energy - T1-4 somatic dysfunction muscle energy technique - First-rib elevation dysfunction articulation - Submandibular myofascial release - Counterstrain technique	Light touch	OMT: NR Sham: 5 min	3 sessions/week	9 (3 weeks)
Schwerla et al., 2008 [41]	- HVLA techniques - Muscle energy techniques - Myofascial release techniques - Balanced ligamentous tension - Visceral techniques - Cranial techniques	Placebo ultrasound	OMT: 45 m Sham: 12 m	OMT: 1 session every 12–20 days Sham 1 session every 4 to 10 days	9 (NR)
Auger et al., 2021 [44]	- Regional thoracic myofascial release - Lumbar soft tissue - Psoas, piriformis, quadratus lumborum counterstrain - Lumbosacral myofascial release - Sacrum balanced ligamentous tension - Lumbar muscle energy	Light touch	NR	3 sessions/week	9 (3 weeks)
Nguyen et al., 2021 [43]	- Articular techniques - HVLA techniques - Balanced ligamentous tension technique - Cranial techniques - Counterstain techniques - Muscle energy techniques - Myofascial release - Visceral techniques	Light touch	45 m	1 session each 2 weeks	6 (12 weeks)
Hensel et al., 2015 [49]	- Thoracic articulation - Cervical soft tissue - Atlanto–occipital decompression - Thoracic inlet myofascial release - Scapulothoracic soft tissue - Lumbar soft tissue - Diaphragm myofascial release	Placebo ultrasound	NR	Sessions at weeks 30, 32, 34, 36, 37, 38, 39	7 (10 weeks)

	- Sacro-iliac articulation - Pubic symphysis decompression - Frog leg sacral release - Compression of the fourth ventricle				
Licciardone et al., 2013 [47]	- HVLA techniques - Moderate-velocity, moderate-amplitude thrusts - Soft tissue stretching - Myofascial release	Light touch	15 m	Sessions at weeks 0, 1, 2, 4, 6, and 8	16 (8 weeks)
Licciardone et al., 2010 [48]	- Range-of-motion mobilization - Muscle energy - Myofascial release - Soft tissue techniques	Placebo ultrasound	30 m	Sessions at weeks 30, 32, 34, 36, 37, 38, 39	7 (10 weeks)
Licciardone et al., 2003 [46]	- Myofascial release - Strain–counterstrain - Muscle energy - Soft tissue - HVLA - Cranial–sacral	Light touch and sham OMT	15–30 m	Sessions at weeks 1, 2, and then monthly	7 (24 weeks)
Gibson et al., 1985 [45]	- Soft tissue manipulation - Passive articulation of stiff spinal segments - HVLA	Placebo short-wave diathermy	NR	1 session/week	4 (4 weeks)

OMT: osteopathic manipulative treatment; NR: not reported.

The outcome variables were pain intensity, disability, and quality of life. The instruments used to measure these outcome variables in each study are listed in Table 1. Pain intensity was assessed using either the visual analog scale (VAS) or the numeric rating scale (NRS). Disability was evaluated with instruments such as the Neck Disability Index (NDI), Quebec Back Pain Disability Index (QBPDI), Oswestry Disability Index (ODI), and Roland Morris Disability Questionnaire (RMDQ). Quality of life was measured using the Short Form-12 or -36 Health Surveys (SF-12, SF-36). All studies measured these outcome variables both at baseline and after the intervention.

3.2. Methodological Quality

The assessment of methodological quality showed that three studies scored four or five points on the PEDro scale and were classified as having fair methodological quality [42,44,45]. Six studies scored between six to eight points and were rated as having good methodological quality [43,49]. One of the most common methodological flaws was that no study blinded the therapist administering the intervention, which is difficult in studies of manual therapy. Additionally, most studies failed to blind participants and did not perform an intention-to-treat analysis. The PEDro scale scores for all studies are shown in Table 3.

Table 3. PEDro scale scores.

Author	Items											Total
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Neck pain												
Palmer et al., 2023 [42]	Y	Y	N	Y	N	N	Y	Y	N	N	N	4/10
Schwerla et al., 2008 [41]	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	7/10
Low-back pain												
Auger et al., 2021 [44]	Y	Y	N	Y	Y	N	N	Y	N	N	N	4/10
Nguyen et al., 2021 [43]	Y	Y	Y	Y	Y	N	N	N	N	Y	Y	6/10
Hensel et al., 2015 [49]	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	7/10

Licciardone et al., 2013 [47]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	8/10
Licciardone et al., 2010 [48]	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8/10
Licciardone et al., 2003 [46]	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	8/10
Gibson et al., 1985 [45]	Y	Y	N	Y	N	N	Y	Y	N	N	Y	5/10

1, eligibility criteria; 2, random allocation; 3, concealed allocation; 4, similarity at baseline; 5, blinding of participants; 6, blinding of therapists; 7, blinding of assessors; 8, measures of at least one key outcome from at least 85% of participants initially allocated to groups; 9, intention to treat analysis; 10, between-group comparison; 11, point measures and measures of variability. 1 = Yes (1 point), 0 = No (0 point), maximum score = 10 (criterion 1 is not included in scores).

3.3. Synthesis of Results

3.3.1. Pain Intensity

In the qualitative synthesis, eight out of nine studies assessing pain intensity did not report statistically significant differences between both groups. Only one study achieved statistically significant improvements in favor of the OMT group [47]. The study conducted by Schwerla et al. measured average pain, worst pain, and best pain, and found statistically significant differences in favor of the OMT group only for average pain [41]. The quantitative analysis (meta-analysis) showed that OMT is not statistically superior to sham or placebo interventions in improving pain intensity (Standardized Mean Difference [SMD] = −0.15; −0.38, 0.08; seven studies; 1173 patients), neither for NP (SMD = −0.42; −1.24, 0.41; two studies; 55 patients) nor for LBP (SMD = −0.10; −0.34, 0.08; five studies; 1118 patients) (Figure 2). The certainty of the evidence was downgraded to very low for patients with NP and to low for patients with LBP (Appendix C).

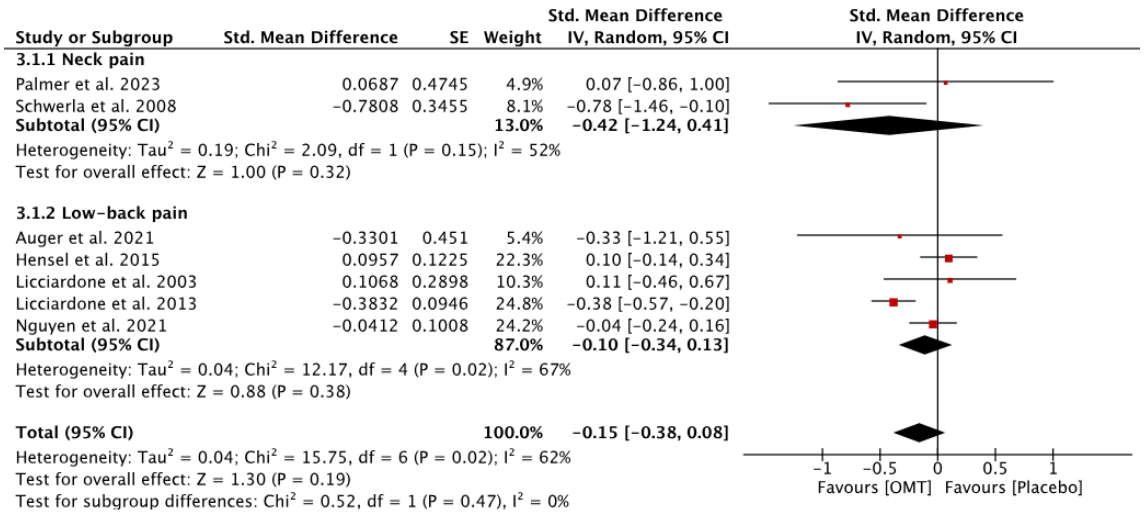

Figure 2. Forest plot for pain intensity in NP and LBP [41−44,46,47,49].

3.3.2. Disability

In the qualitative synthesis, six studies out of seven assessing disability did not report statistically significant differences between both groups. Only the study of Nguyen et al. showed statistically significant differences in favor of the OMT group for disability [43]. The quantitative analysis (meta-analysis) showed that OMT is not statistically superior to sham or placebo interventions in improving disability (SMD = −0.09; −0.25, 0.08; six studies; 1153 patients), neither for NP (SMD = −0.24; −1–15, 0.66; two studies; 55 patients) nor for LBP (SMD = −0.07; −0.22, 0.09; four studies; 1098 patients) (Figure 3). The certainty of the evidence was downgraded to very low for patients with NP and moderate for patients with LBP (Appendix C).

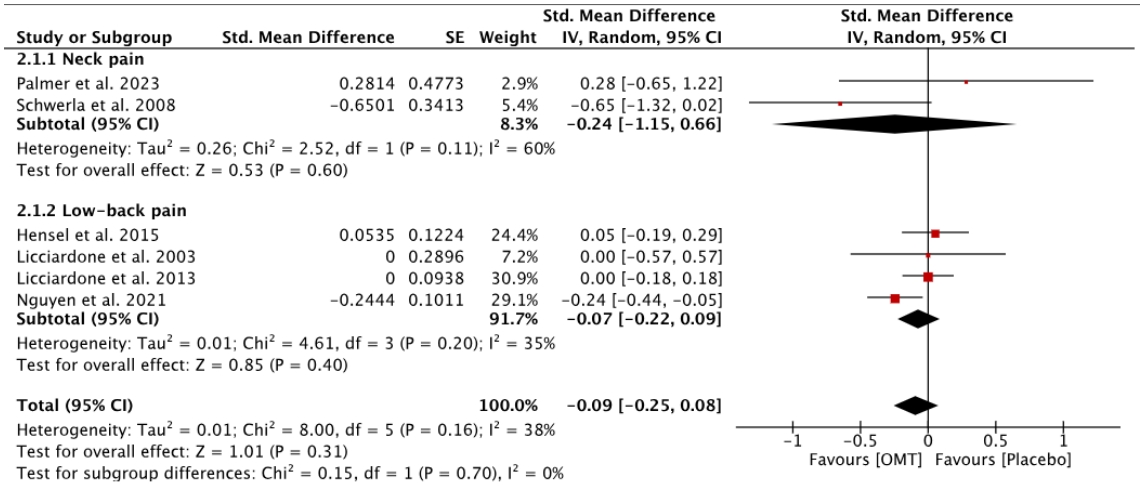

Figure 3. Forest plot for disability in NP and LBP [41–43,46,47,49].

3.3.3. Quality of Life

Six studies assessed quality of life. Two of them used the questionnaire SF-36 and found no statistically significant differences between both groups [46,47]. Three of them assessed only the physical and mental health subscales of the SF-12, reporting no statistically significant differences between both groups [42–44]. Only one study assessed the subscale of bodily pain of the SF-36 and achieved statistically significant differences in favor of the OMT group [41]. No meta-analysis was conducted due to insufficient data in the included studies.

4. Discussion

The aim of this systematic review and meta-analysis was to determine whether OMTs for somatic dysfunctions are more effective than sham or placebo interventions in improving pain intensity, disability, and quality of life in patients with NP or LBP. The qualitative synthesis showed that most studies found no statistically significant differences between both interventions, and the quantitative synthesis supports this finding.

The methodological quality of the included clinical trials was mixed. All of the scores ranged from fair to good quality. The most common methodological flaw was the lack of blinding therapists, which is difficult in manual therapy studies. Thus, these studies are inevitably open to bias. The second most common methodological flaw was the lack of intention-to-treat analysis.

The results of our systematic review and meta-analysis are contrary to those found in previous reviews. However, those reviews had serious methodological issues [12–15]. To avoid the methodological biases identified in earlier studies, our study included only clinical trials published after a peer-review process that applied holistic osteopathic interventions based on a pragmatic diagnosis of somatic dysfunctions, compared with a simulated intervention or placebo. On the other hand, our results are in line with previous systematic reviews with meta-analyses concluding that isolated osteopathic interventions, such as visceral osteopathy [16,50,51] or cranial osteopathy [17,52–54], have no clinical effects on musculoskeletal pathologies. Yet, previous studies have shown that OMT is more effective than no intervention in patients with NP [55,56] or LBP [12,57,58]; however, when compared to other interventions, the effects appear to be smaller. These results are likely due to placebo rather than the specific effects of OMT. In other words, the application of real OMT and sham OMT may produce the same or similar neurophysiological effects in the patients, which explains the lack of statistically significant changes between both groups [59,60].

The studies included were based on individualized osteopathic diagnoses through manual palpation of various somatic dysfunctions. Several authors have demonstrated that these are unreliable [51,54,60,61]. In the case of cranial osteopathy, it has been demonstrated that the manual detection of the primary respiratory mechanism or movement restrictions in the skull are unreliable [54]. As for visceral osteopathy, it has been shown that visceral movement impairment is not related to the origin of pathologies, and the palpation of the movement or tension of the viscera is unreliable [51]. Regarding myofascial release, only post-surgical or post-traumatic studies have demonstrated the presence of fascial restrictions or adhesions, and the force required to modify these tissues cannot be achieved manually [62]. Other studies have raised concerns about the reliability of manual palpation for detecting hypomobile segments in the spine. Therapists often misidentify vertebral levels, typically deviating by at least one segment, which increases the risk of misclassification and reduces the diagnostic validity of these methods [63]. It follows that the individualized diagnosis of somatic dysfunctions presents serious limitations in terms of validity and reliability.

Our review has several limitations. Firstly, the searches were conducted in the most relevant databases; however, some studies not indexed in these sources may have been missed. Secondly, the diverse NP and LBP diagnosis, as well as the lack of data reported by some studies, complicates the interpretation of the results and may weaken our conclusion. Thirdly, the primary studies pragmatically applied interventions based on diagnoses of various somatic dysfunctions, resulting in a high degree of heterogeneity among the treatments applied.

5. Conclusions

The findings of this systematic review and meta-analysis reveal that OMT is not superior to sham or placebo interventions for improving pain intensity, disability, and quality of life in patients with NP or LBP.

Author Contributions: Conceptualization, E.E. and L.C.-L.; methodology, E.E. and L.C.-L.; software, L.C.-L. and S.J.-d.-B.; formal analysis, L.C.-L. and S.J.-d.-B.; resources, L.C.-L. and S.J.-d.-B.; data curation, L.C.-L., R.M.-d.-l.-F., R.R.-P. and A.C-U.; writing—original draft preparation, L.C.-L., S.J.-d.-B., R.M.-d.-l.-F., R.R.-P. and A.C-U.; writing—review and editing, E.E.; visualization, L.C.-L., S.J.-d.-B., R.M.-d.-l.-F., R.R.-P. and A.C.-U.; supervision, E.E.; project administration, L.C-L. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A. Detailed Search Strategy According to the PRISMA Model

Search terms

Population	Intervention	Comparator	Study
Back pain	Osteopathic manipulation	Sham	Clinical trial
Low-back pain	Osteopathic medicine	Placebo	Controlled clinical trial
Sciatica	Osteopathic treatment	Simulated	Randomized controlled trial
Low-back ache	Osteopathic intervention		Trial
Mechanical low-back pain	Osteopathic manipulative treatment		
Lumbago			
Lower back pain			
Low-back ache			
Low-back ache			
Postural low-back pain			
Neck pain			
Chronic neck pain			
Mechanical neck pain			
Non-specific neck pain			

Non-specific chronic neck pain

PUBMED
(((manipulation, osteopathic[MeSH Terms] OR medicine, osteopathic[MeSH Terms] OR "osteopathic medicine" OR "osteopathic treatment" OR "osteopathic manipulation" OR "osteopathic intervention" OR "osteopathic manipulative treatment" OR osteopath*) AND (neck pain[MeSH Terms] OR "neck pain" OR "chronic neck pain" OR ·"mechanical neck pain" OR "non-specific neck pain" OR "non-specific chronic neck pain" OR low back pain[MeSH Terms] OR back pain[MeSH Terms] OR sciatica[MeSH Terms] OR low back ache[MeSH Terms] OR mechanical low back pain[MeSH Terms] OR "back pain" OR "low back pain" OR sciatica OR lumbago OR "lower back pain" OR "low back ache" OR low backache OR "postural low back pain" OR "mechanical low back pain")) AND (placebo OR sham OR simulated)))
Results: 96
Data: 29 September 2024

PEDro
osteopathic OR osteopathy
Results: 31
Data: 29 September 2024

Cochrane Library
((manipulation, osteopathic OR medicine, osteopathic OR "osteopathic medicine" OR "osteopathic treatment" OR "osteopathic manipulation" OR "osteopathic intervention" OR "osteopathic manipulative treatment" OR osteopath*) AND (neck pain OR "neck pain" OR "chronic neck pain" OR ·"mechanical neck pain" OR "non-specific neck pain" OR "non-specific chronic neck pain" OR low back pain OR back pain OR sciatica OR low back ache OR mechanical low back pain OR "back pain" OR "low back pain" OR sciatica OR lumbago OR "lower back pain" OR "low back ache" OR low backache OR "postural low back pain" OR "mechanical low back pain") AND (placebo OR sham OR simulated))
Results: 89
Data: 29 September 2024

Web of Science
(manipulation, osteopathic OR medicine, osteopathic OR "osteopathic medicine" OR "osteopathic treatment" OR "osteopathic manipulation" OR "osteopathic intervention" OR "osteopathic manipulative treatment" OR osteopath*) (Topic) and (neck pain OR "neck pain" OR "chronic neck pain" OR ·"mechanical neck pain" OR "non-specific neck pain" OR "non-specific chronic neck pain" OR low back pain OR back pain OR sciatica OR low back ache OR mechanical low back pain OR "back pain" OR "low back pain" OR sciatica OR lumbago OR "lower back pain" OR "low back ache" OR low backache OR "postural low back pain" OR "mechanical low back pain") (Topic) and (placebo OR sham OR simulated) (Topic)
Results: 160
Data: 29 September 2024

Appendix B. Excluded Studies

Author	Reason for Exclusion
Licciardone, J.C.; Aryal, S. Clinical Response and Relapse in Patients with Chronic Low Back Pain Following Osteopathic Manual Treatment: Results from the OSTEOPATHIC Trial. *Man Ther* **2014**, *19*, 541–548, https://doi.org/10.1016/j.math.2014.05.012. [27]	Secondary analyses of the OSTEOPATHIC trial conducted by Licciardone et al. excluded to avoid data duplication.

Licciardone, J.C.; Gatchel, R.J.; Aryal, S. Targeting Patient Subgroups with Chronic Low Back Pain for Osteopathic Manipulative Treatment: Responder Analyses from a Randomized Controlled Trial. *Journal of the American Osteopathic Association* **2016**, *116*, 156–168, https://doi.org/10.7556/jaoa.2016.032. [28] Licciardone, J.C.; Gatchel, R.J.; Aryal, S. Recovery from Chronic Low Back Pain after Osteopathic Manipulative Treatment: A Randomized Controlled Trial. *Journal of the American Osteopathic Association* **2016**, *116*, 144–155, https://doi.org/10.7556/jaoa.2016.031. [29] Licciardone, J.C.; Kearns, C.M.; Crow, W.T. Changes in Biomechanical Dysfunction and Low Back Pain Reduction with Osteopathic Manual Treatment: Results from the OSTEOPATHIC Trial. *Man Ther* **2014**, *19*, 324–330, https://doi.org/10.1016/j.math.2014.03.004. [30] Licciardone, J.C.; Kearns, C.M.; Minotti, D.E. Outcomes of Osteopathic Manual Treatment for Chronic Low Back Pain According to Baseline Pain Severity: Results from the OSTEOPATHIC Trial. *Man Ther* **2013**, *18*, 533–540, https://doi.org/10.1016/j.math.2013.05.006. [31] Licciardone, J.C.; Kearns, C.M.; Hodge, L.M.; Bergamini, M.V.W. Associations of Cytokine Concentrations With Key Osteopathic Lesions and Clinical Outcomes in Patients With Nonspecific Chronic Low Back Pain: Results From the OSTEOPATHIC Trial. *Journal of American Osteopathic Association* **2012**, *112*, 596–605. [32] Licciardone, J.C.; Kearns, C.M. Somatic Dysfunction and Its Association With Chronic Low Back Pain, Back-Specific Functioning, and General Health: Results From the OSTEOPATHIC Trial. *Journal of American Osteopathic Association* **2012**, *112*, 420–428. [33] Licciardone, J.C.; Gatchel, R.J.; Kearns, C.M.; Minotti, D.E. Depression, Somatization, and Somatic Dysfunction in Patients with Nonspecific Chronic Low Back Pain: Results from the OSTEOPATHIC Trial. *J Am Osteopath Assoc* **2012**, *112*, 783–791. [34]	
Hensel, K.L.; Pacchia, C.F.; Smith, M.L. Acute Improvement in Hemodynamic Control after Osteopathic Manipulative Treatment in the Third Trimester of Pregnancy. *Complement Ther Med* **2013**, *21*, 618–626, https://doi.org/10.1016/j.ctim.2013.08.008. [35] Hensel, K.L.; Roane, B.M.; Chaphekar, A.V.; Smith-Barbaro, P. PROMOTE Study: Safety of Osteopathic Manipulative Treatment during the Third Trimester by Labor and Delivery Outcomes. *Journal of the American Osteopathic Association* **2016**, *116*, 698–703, https://doi.org/10.7556/jaoa.2016.140. [36]	Secondary analyses of the PROMOTE study conducted by Hensel et al. excluded to avoid data duplication.
Ajimsha, M.S.; Daniel, B.; Chithra, S. Effectiveness of Myofascial Release in the Management of Chronic Low Back Pain in Nursing Professionals. *J Bodyw Mov Ther* **2014**, *18*, 273–281, https://doi.org/10.1016/j.jbmt.2013.05.007. [37]	Application of a single osteopathic technique without conducting a holistic assessment of the patients' somatic dysfunctions. Therefore, it does not meet the eligibility criteria for this study.
Klein, R.; Bareis, A.; Schneider, A.; Linde, K. Strain-Counterstrain to Treat Restrictions of the Mobility of the Cervical Spine in Patients with Neck Pain-A Sham-Controlled Randomized Trial. *Complement Ther Med* **2013**, *21*, 1–7, https://doi.org/10.1016/j.ctim.2012.11.003. [38]	Application of a single osteopathic technique without conducting a holistic assessment of the patients' somatic dysfunctions. Therefore, it does not meet the eligibility criteria for this study.
Guthrie, R.A.; Bedford, D.; Ralph Martin, T.H. Effect of Pressure Applied to the Upper Thoracic (Placebo) versus Lumbar Areas	Application of a single osteopathic technique without conducting a holistic assessment of

(Osteopath Ic Manipula Tive Treatment) for Inhibition of Lumbar Myalgia during Labor. *J Am Osteopath Assoc* **1982**, *82*, 247–251. [39]	the patients' somatic dysfunctions. Therefore, it does not meet the eligibility criteria for this study.
Williams, N.H.; Wilkinson, C.; Russell, I.; Edwards, R.T.; Hibbs, R.; Linck, P.; Muntz, R. Randomized Osteopathic Manipulation Study (ROMANS): Pragmatic Trial for Spinal Pain in Primary Care. Fam Pract 2003, 20, 662–669, https://doi.org/10.1093/fampra/cmg607. [40]	Inclusion of patients with NP and LBP without differentiated data between the two types of patients, which does not allow for its inclusion in either qualitative or quantitative analysis.

Appendix C. Certainty of Evidence with GRADEPro

Certainty of Evidence							Patients		Effect		Certainty
Nº of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness Evidence	Imprecision	Others	[OMT]	[Placebo]	Relative (95% CI)	Absolute (95% CI)	
Pain intensity (VAS or NPRS) in NP											
2	RCTs	Serious [a]	Serious [b]	Serious [c]	Very serious [d]	None	31	24	-	SMD −0.42; (−1.24, 0.41)	⊕◯◯◯ Very low
Disability (NDI, ODI or RMDQ) in NP											
2	RCTs	Serious [a]	Serious [b]	Serious [c]	Very serious [d]	None	31	24	-	SMD −0.24 (−1.15, 0.66)	⊕◯◯◯ Very low
Pain intensity (VAS or NPRS) in LBP											
5	RCTs	Not serious	Serious [b]	Serious [c]	Not serious	None	588	546	-	SMD −0.10; (−0.38, 0.13)	⊕⊕◯◯ Low
Disability (NDI, ODI or RMDQ) in LBP											
4	RCTs	Not serious	Not serious	Serious [c]	Not serious	None	578	536	-	SMD −0.07 (−0.22, 0.09)	⊕⊕⊕◯ Moderate

CI: confidence interval; SMD: standardized mean difference. Explanations: [a] More than 25% of the participants were from studies with poor or fair methodological quality, considering the following aspects: lack of allocation concealment, random allocation and/or sample size calculation, participant and personnel blinding, blinding of outcome assessors. [b] I^2 level was higher than 50%. [c] Indirectness was downgraded because the interventions were heterogeneous. [d] Population included in each group < 30 participants. High: We are very confident that the true effect is close to the estimate of the effect. Moderate: We are moderately confidence in the effect estimate. The true effect is close to the estimate of the effect, but the result can be different. Low: Confidence in the effect estimate is limited, and the true effect can be substantially different from the estimate of the effect. Very Low: There is little confidence in the effect estimate, and the true effect is likely to be substantially different from the estimated effect.

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Clinical effectiveness of visceral osteopathy. A systematic review with meta-analysis.

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Abstract:	Objective : the aim of this systematic review with meta-analysis aims to evaluate the clinical effectiveness of visceral osteopathy (VO) in musculoskeletal and non-musculoskeletal disorders. Methods: two independent reviewers searched in PubMed, Physiotherapy Evidence Database, Cochrane Library, Scopus, and Web of Science databases in November 2023 and extracted data for randomized controlled trials evaluating the clinical effectiveness of VO. The risk of bias and the certainty of evidence were assessed using the Risk-of-Bias tool 2 and the GRADE Profile, respectively. Meta-analyses were conducted using random effect models using RevMan 5.4. software. Results: Fifteen studies were included in the qualitative and seven in the quantitative synthesis. For musculoskeletal disorders, the qualitative and quantitative synthesis suggested that VO produces no statistically significant changes in any outcome variable for patients with low back pain, neck pain or urinary incontinence. For non-musculoskeletal conditions, the qualitative synthesis showed that VO was not effective for the treatment of irritable bowel syndrome, breast cancer, and very low weight preterm infants. Most of the studies were classified as high risk of bias and the certainty of evidence downgraded to low or very low. Conclusion: VO did not show any benefit in any musculoskeletal or non-musculoskeletal condition.
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Is visceral osteopathy therapy effective? A systematic review and meta-analysis

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Clinical effectiveness of visceral osteopathy. A systematic review with meta-analysis.

ABSTRACT

Objective: the aim of this systematic review with meta-analysis aims to evaluate the clinical effectiveness of visceral osteopathy (VO) in musculoskeletal and non-musculoskeletal disorders.

Methods: two independent reviewers searched in PubMed, Physiotherapy Evidence Database, Cochrane Library, Scopus, and Web of Science databases in November 2023 and extracted data for randomized controlled trials evaluating the clinical effectiveness of VO. The risk of bias and the certainty of evidence were assessed using the Risk-of-Bias tool 2 and the GRADE Profile, respectively. Meta-analyses were conducted using random effect models using RevMan 5.4. software.

Results: Fifteen studies were included in the qualitative and seven in the quantitative synthesis. For musculoskeletal disorders, the qualitative and quantitative synthesis suggested that VO produces no statistically significant changes in any outcome variable for patients with low back pain, neck pain or urinary incontinence. For non-musculoskeletal conditions, the qualitative synthesis showed that VO was not effective for the treatment of irritable bowel syndrome, breast cancer, and very low weight preterm infants. Most of the studies were classified as high risk of bias and the certainty of evidence downgraded to low or very low.

Conclusion: VO did not show any benefit in any musculoskeletal or non-musculoskeletal condition.

Keywords: complementary therapies; osteopathy; visceral manipulation; systematic review; meta-analysis.

INTRODUCTION

Visceral osteopathy (VO) was developed in the 1980s by the French osteopaths Jean-Pierre Barral and Pierre Mercier and is defined as an intervention based on a manual mobilization (commonly known as visceral manipulation) that allegedly restores the mobility and the function of the viscera, normalizing the excitability state of the afferent neurons of the central nervous system (Barral & Mercier, 2004). It has been categorized as a complementary and alternative therapy by the World Health Organization (WHO) and included in the Benchmarks for Osteopathic Education of the WHO (World Health Organization, 2010).

The rationale use of VO, according to its proponents is that the mobility of the viscera create abnormal tension patterns and chronic irritation leading to functional and structural problems throughout the body resulting a range of conditions such as low back pain, neck pain, irritable bowel syndrome, constipation, urinary incontinence, dyspepsia, or gastroesophageal reflux among others (Attali et al., 2013; De Marco et al., 2022; Eguaras et al., 2019; Pasin Neto & Borges, 2020; Tamer et al., 2017; Tozzi et al., 2011, 2012). Between 23.6% to 62.4% of osteopaths seem to use VO always or often (Alvarez et al., 2020; Rui et al., 2022; van Dun, Arcuri, et al., 2022; van Dun, Verbeeck, et al., 2022); and 17.2% to 28% use it as a first-line treatment (Álvarez-Bustins et al., 2018; Leach et al., 2019).

The viscera clearly do move during breathing or activities such as running and jumping (Cazzola et al., 2014). However, the notion that an impairment of these motions causes or aggravates the above-named conditions is of questionable biological plausibility (Hidalgo et al., 2024). Moreover, the validity of the diagnostic techniques used in VO is doubtful. Guillaud et al.(Guillaud et al., 2018) reviewed eight studies testing the intra- and inter-rater reliability of visceral diagnostic techniques and concluded that these techniques were not reliable.

The clinical effectiveness of VO has been tested in a growing number of clinical trials. The systematic review conducted by Switters et al. (Switters et al., 2019) suggested that VO may be

a promising intervention for patients with low back pain. However, a more recent meta-analysis questioned this conclusion results (Ceballos-Laita et al., 2023). Muller et al. (Müller et al., 2014) and Lotfi et al. (Lotfi et al., 2023) found that VO might be beneficial for patients with irritable bowel syndrome. However, two recent systematic reviews recently suggested the use of VO in non-musculoskeletal disorders is not supported by sound evidence (Buffone et al., 2023; F. C. da Silva et al., 2023). These contradictions might be due to the inclusion of primary studies in the reviews that apply multimodal interventions in which the effects of VO were obscured. Several further randomized clinical trials (RCTs) of VO have recently emerged that might resolve the contradictions. Thus, the aim of this systematic review with meta-analysis is to critically evaluate the totality of the evidence for or against the effectiveness of VO as a treatment of musculoskeletal and non-musculoskeletal disorders.

METHODS

Study design

This systematic review with meta-analysis was conducted following the PRISMA statement and the Cochrane recommendations (Page et al., 2021). The protocol of this review was prospectively registered in PROSPERO (identification number CRD42023485627).

Search strategy

The bibliographical searches were carried out in PubMed (MEDLINE), Physiotherapy Evidence Database (PEDro), Cochrane Library, Web of Science (WOS), and SCOPUS from inception to November 2023. Medical Subject Heading (MeSH) terms and grey terms were used as keywords in the search strategy: “visceral manipulation”, “visceral mobilization”, “visceral osteopathy” among others. The search strategy used in each database is shown in the Appendix I. The reference lists of the included studies and the above-mentioned previous systematic reviews were hand-searched.

Eligibility criteria and study selection

To be included studies had to meet the following inclusion criteria based on the PICOS method:

Population: the population of interest was patients with musculoskeletal or non-musculoskeletal conditions.

Intervention: the intervention of interest was VO applied as a sole therapy or in addition to a standard care based on non-pharmacological conservative techniques.

Comparison: the intervention of interest had to be compared to a sham, control, or the same standard care based on non-pharmacological conservative techniques.

Outcome(s): the studies had to reported variables related to the clinical effectiveness of VO.

Study design: RCT or cross-over designs.

Studies were excluded if they: included healthy participants; applied a multimodal intervention or comparator in which the effects of VO could not be extrapolated (i.e. craniosacral therapy, joint manipulation, and VO as a multimodal intervention); reported no clinical outcomes or variables related to the status of the patient, or the outcome measures were not quantified using validated instruments.

The reference lists retrieved from each database were exported to Mendeley to remove duplicates. Two authors (LC and SJ) independently reviewed the title and abstract of each retrieved study to determine their potential eligibility. The studies that met the eligibility criteria were assessed in full text by the same authors. A third author (AC) was consulted in case of discrepancies.

Data extraction

The data extraction was performed independently by two reviewers (LC and SJ) using a predetermined sheet adapted from the Cochrane Collaboration. The data extracted were the

characteristics of the population (mean age, diagnosis), type of interventions (session duration, sessions per week, and total number of sessions), outcome variables, and results. Data were analyzed using a qualitative and quantitative synthesis.

Risk of bias assessment

The risk of bias was assessed using the Cochrane risk-of-bias-tool 2 (RoB2) The same authors performed independently the assessment.

The RoB2 was used to determine the potential risk of bias in RCTs and consist of five questions that assess the following types of bias: risk of bias arising from the randomization process (domine 1), risk of bias due to deviations from the intended interventions (domain 2), risk of bias due to missing outcome data (domain 3), risk of bias in measurement of the outcome (domain 4), and risk of bias in selection of the reported result (domain 5). The responses to signaling questions can be “low”, “unclear” or “high” for each domain. The official instructions from the Cochrane Collaboration were used to ensure the answer to each question (Higgins et al., 2011). A study is judged to be low risk of bias if all criteria were met, a study was considered as unclear risk of bias when at least one item presented some concerns, and a study was judged to be high risk of bias when at least one item was considered as high risk (Higgins et al., 2022).

Data synthesis and analysis

A qualitative synthesis of the results was conducted and whenever was possible, a quantitative synthesis (meta-analysis) was carried out using the RevMan 5.4 software.

Data were combined for meta-analysis when at least two studies were sufficiently homogeneous. Studies were considered homogeneous if they applied a common intervention and measured a common outcome. Mean, standard deviations (SD), and sample size at each time point were extracted for each group. When mean and SD were not reported in the manuscript, the corresponding authors were contacted by email asking the raw data. Outcomes

were analyzed based on the post-intervention means and SDs by calculating the mean difference (MD) when RCTs used the same scale or standardized mean difference (SMD) when they used different scales, with 95% coefficient intervals (CIs). SMD classifies the effects estimates as small (SMD at least 0.2 but less than 0.5), medium (SMD from 0.5 to less than 0.8), or large (SMD 0.8 or greater) (Cohen, 1988). Significance was set at a P value <0.05.

Random-effect meta-analysis was performed when the combination of intervention effects could incorporate an assumption that the studies are not all estimating the same intervention effect (Higgins et al., 2019). The heterogeneity was assessed considering the similarity of point estimates, overlap of confidence intervals, the context of the results and the I^2 statistic in the forest plots (Guyatt et al., 2023; Schünemann HJ et al., 2023). To detect publication bias and to test each study's influence, we visually examined the forest plot and performed an exclusion sensitivity analysis. Funnel plots were not reported because any meta-analysis met the rule of at least 10 trials included in each forest plot.

Certainty of evidence assessment

The certainty of evidence was assessed by GRADE Evidence Profiles by the same independent reviewers. The categories of evidence were classified as "high", "moderate", "low", or "very low", to help researchers and clinicians on the importance of the results. The certainty was assessed according to the following domains: risk of bias, inconsistency, indirectness, imprecision, and other considerations.

The certainty of evidence was downgraded in accordance of the presence of the following: risk of bias (downgraded by one level if at least 25% of the participants were from studies with high risk of bias; and two levels if at least 50% of the participants were from studies with high risk of bias: lack of allocation concealment, random allocation and/or sample size calculation, participant, and personnel blinding, blinding of outcome assessors), inconsistency of results (downgraded by one level or two levels according to the similarity of point estimates, overlap of

confidence intervals, the I^2 statistic that are considered moderate if I^2 is ≥50% and large if is ≥75%, and the context of the results)(Guyatt et al., 2023; Schünemann HJ et al., 2023), indirectness of evidence (downgraded by one level if different populations, interventions, or comparators were included), and imprecision (downgraded by one or two levels if sample size were small and the confidence intervals were wide) (Schünemann et al., 2022; Schünemann HJ et al., 2023). Single randomized trials were considered inconsistent and imprecise and provided "low certainty" evidence. This could be further downgraded to "very low" certainty if there was also a high risk of bias (Higgins et al., 2011; Xie & Machado, 2021).

RESULTS

Our searches found 295 papers, after studying their abstracts, 18 RCTs were selected for full-text review of which three were excluded: two used multi-interventions from which the effects of VO could not be extrapolated (Florance et al., 2012; Hundscheid et al., 2007), and one did not present sufficient data to evaluate the clinical effectiveness of VO (Pasin Neto & Borges, 2020). Fifteen RCTs were included in the qualitative synthesis and seven could be included in the meta-analysis (quantitative synthesis). The description of the selection process is shown in the PRISMA flowchart diagram (Figure 1).

Characteristics of the included studies

The characteristics of the included studies are shown in the Table 1. All the studies included were published between 2012 and 2023. All the studies were designed as RCTs with parallel groups, except one that had a cross-over design (Attali et al., 2013). The total sample size of all the studies was 742, of which 418 were from the VO group, and 324 were from the control group.

Risk of bias assessment

The overall risk of bias was considered to be high for 11 studies, two studies presented some concerns, and two studies were classified as low risk of bias. The figure 2 showed in detail the Cochrane risk-of-bias 2 tool results.

Clinical effectiveness on musculoskeletal conditions

Nine studies were included evaluating the clinical effectiveness of VO in patients with musculoskeletal conditions such as low back pain, neck pain and urinary incontinence due to pelvic floor muscle dysfunction. Pain intensity or symptoms were the most frequently used outcome measures, five studies assessed disability, four assessed spine flexion range of motion, and two kidney mobility.

In the qualitative synthesis, three out of nine studies assessing pain intensity reported statistically significant improvements in favor to the VO group (Altınbilek et al., 2023; Lo Basso et al., 2021; Tozzi et al., 2012). Two out of five studies assessing disability reported improvements in disability in favor to the VO group (Altınbilek et al., 2023; Boas Fernandes et al., 2023). One out of four studies reported improvements in spinal range of motion in favor to the VO group (Villalta Santos et al., 2019). Two out of two studies reported an improvement in kidney mobility after VO (Lo Basso et al., 2021; Tozzi et al., 2012) (Table 1).

In the quantitative synthesis, no statistically significant differences were found for pain intensity (SMD: 0.46; 95%CI: -0.93, 0.02; 361 patients), disability (SMD: -0.16; 95%CI: -0.85, 0.52; 197 patients), flexion range of motion (SMD: -0.20; 95%CI: -0.15, 0.55; 144 patients), physical function (SMD: -0.26; 95%CI: -0.62, 0.10; 121 patients), or kidney mobility (MD: 3.38; 95%CI: -2.13, 8.89; 160 patients) (Figure 3 A-E).

The certainty of evidence was downgraded to low for range of motion and physical function and to very low for pain intensity, disability, and kidney mobility (table 2).

Clinical effectiveness for non-musculoskeletal conditions

Six studies were included evaluating the clinical effectiveness of VO in patients with non-musculoskeletal conditions such as irritable bowel syndrome, breast cancer, very low birth weight infants, gastrointestinal reflux, and polycystic ovarian syndrome (table 1).

Attali et al. (Attali et al., 2013) applied VO in patients with irritable bowel syndrome and found a statistically significant improvement in rectal sensitivity but not in constipation, diarrhea, abdominal distension, abdominal pain, or colonic transit time compared to a sham intervention. EL-Din Hammam et al. (Essam et al., 2022) found an improvement in abdominal distension, girth, depression, and anxiety after applying VO compared to a control group.

Lagrange et al. (Lagrange et al., 2019) found no statistically significant improvements in any outcome variable (nausea, constipation, and quality of life) after applying VO in women operating on breast due to breast cancer.

Haiden et al. (Haiden et al., 2015) compared VO to no additional intervention for the meconium excretion, feeding, duration of the stay and weight but no statistically significant differences were found. A significant worsening was observed in full enteral feeding.

Eguaras et al. (Eguaras et al., 2019) applied VO in patients with gastroesophageal reflux and found an improvement in the symptoms, pressure pain threshold and cervical mobility compared to sham VO.

Yosri et al. (Yosri et al., 2022) compared VO with a low-calorie diet vs low-calorie diet in isolation for women with polycystic ovarian syndrome and found between-groups differences only in ovarian symptoms in favor to the VO group, but no changes were found in weight or body mass index.

The quantitative synthesis was not carried out due to the high heterogeneity in the populations and outcome variables assessed.

<u>High versus low quality studies</u>

Studies with higher risk of bias tended to demonstrate statistically significant differences in favor to the VO group, while the studies with lower risk of bias tended to show no such differences. In musculoskeletal conditions, the studies that were classified as high risk of bias and presented more domains classified as high risk of bias found statistically significant differences in favor to the VO group in all the outcome variables (Altınbilek et al., 2023; Lo Basso et al., 2021; Tozzi et al., 2012). On the other hand, two studies classified as high risk of bias but with less domains classified as high risk of bias presented no statistically significant differences in any outcome variable (A. C. D. O. Silva et al., 2018; Tamer et al., 2017). The three studies classified as some concerns did not present statistically significant differences in the primary outcome measure (Boas Fernandes et al., 2023; Panagopoulos et al., 2015; Villalta Santos et al., 2019), and the only study that was classified as low risk of bias (De Marco et al., 2022) showed no statistically significant differences between the VO and the control group.

In non-musculoskeletal conditions, the studies presented as high risk with more domains classified as high risk found statistically significant differences in favor to the VO group in all the outcome variables (Essam et al., 2022; Yosri et al., 2022). The studies with less domains considered as high risk and the only study classified as low risk presented no between-groups differences (Attali et al., 2013; Haiden et al., 2015; Lagrange et al., 2019).

Adverse events

Ten RCTs failed to mention adverse events. Eguaras et al. (Eguaras et al., 2019) reported that two patients in the VO group felt hypersensitivity in the epigastric area after the intervention, De Marco et al. (De Marco et al., 2022) reported that one patient of the VO group experienced abdominal pain for about 48h, and Haiden et al. (Haiden et al., 2015) reported that the infants included in the VO group had a statistically significant longer time to full enteral feedings. Yosri et al. (Yosri et al., 2022) and Panagopoulos et al. (Panagopoulos et al., 2015) assessed adverse events and reported that none had occurred.

DISCUSSION

This systematic review with meta-analysis aimed at determining if VO is clinically effective for musculoskeletal or non-musculoskeletal disorders. Fifteen studies were included in the qualitative synthesis and seven in the quantitative synthesis. For musculoskeletal disorders, most of the studies suggested a lack of clinical effectiveness of VO in all the outcome variables assessed, and the qualitative synthesis supported these results. For non-musculoskeletal conditions, no quantitative synthesis could be analyzed due to the heterogeneity of the studies, but most of the studies suggested that VO was not effective.

In musculoskeletal conditions, more than half of the included studies failed to show statistically significant improvements in the variables evaluated in patients low back pain, neck pain and urinary incontinence due to pelvic floor muscle dysfunction. Five studies showed some improvements after the application of VO in pain intensity, disability, range of motion and/or kidney mobility (Altınbilek et al., 2023; Lo Basso et al., 2021; Tozzi et al., 2012; Villalta Santos et al., 2019; Boas Fernandes et al., 2023). Three of them were classified as high risk of bias (Altınbilek et al., 2023; Lo Basso et al., 2021; Tozzi et al., 2012) and two as some concerns (Villalta Santos et al., 2019; Boas Fernandes et al., 2023). The quantitative synthesis corroborated these results for all the outcome variables. Only the pain intensity in the low back pain subgroup showed a statistically significant improvement in favor of the VO group (SMD: 0.65; 95%CI: -1.28, -0.02). However, these results were only achieved because the study of Tozzi et al. (Tozzi et al., 2012) is an outlier.

The validity of these positive results is, however, questionable. None registered the study protocol prospectively, none adequately described the randomization or the allocation process, and none was double-blind, even though the authors affirmed otherwise, because the masking of the placebo technique was not evaluated or because the outcomes were self-registered by patients instead of by blinded examiners. Further methodological flaws include the following

Altinbilek et al.(Altınbilek et al., 2023) did not analyze their data using an intention-to-treat analysis despite six dropouts. Statistical analysis did not allow a correct interpretation of the results because data were presented as median instead of mean and standard deviation. Tozzi et al.(Tozzi et al., 2012) included 140 patients and randomized 109 to the experimental group and only 31 to the control group. Lo Basso et al.(Lo Basso et al., 2021) did not control medication intake and employed an inadequate statistical analysis.

The therapists that carried out the VO claimed high palpatory skills. The ability to find restrictions, increased tensions, or malposition in the viscera or fascial tissues surrounding the viscera allegedly allowed them to conduct targeted manual interventions and affecting tissues such as muscles or joints because of the myofascial continuity (Tozzi et al., 2012). These anatomic possibilism is used by osteopaths to elaborate osteopathic diagnostic explanations and works for clinical assessment and treatment, but these relationships have shown to be implausible (Hidalgo et al., 2024).

In non-musculoskeletal conditions, a quantitative synthesis was not performed due to the heterogeneity of the studies included, but in the qualitative synthesis two studies found benefits applying VO in patients with irritable bowel syndrome and gastroesophageal reflux after two to three sessions in the short term compared to a sham VO. And three studies did not find benefits applying VO in patients with irritable bowel syndrome, symptoms related to breast cancer, or meconium excretion in very low birth weight infants. The risk of bias assessments showed that the positive studies were also those burdened with the highest risk of bias, while the negative studies were less biased.

The two studies that presented statistically significant differences were severely flawed. The study of El-Din Hammam et al.(Essam et al., 2022) did not present information about the randomization process nor the allocation concealment, the examiners and participants were not blinded, and a prospective register or protocol to compare the data presented in the study was

not provided. The study of Eguaras et al. (Eguaras et al., 2019) claimed that participants and examiners were blinded. But it was not evaluated whether the blinding had been successful. Furthermore, the primary outcome was self-reported, which means that its evaluation was not blind, medication intake was not controlled for, and patients' expectations were not considered.

Overall, our results are in accordance with previous systematic reviews revealing a lack of compelling evidence for VO (Buffone et al., 2023; F. C. da Silva et al., 2023). Concerning the methodological quality of the fifteen included RCTs, it is worth considering that trials of non-pharmacological conservative interventions can be complex. The use of patient-reported outcomes is highly recommended by clinical guidelines in patient-centered interventions, but it may introduce to bias. Moreover, in trials of manual interventions cannot be blinded.

Ten RCTs did not mention adverse events at all. This omission is strictly speaking a violation of research ethics and highlights the generally low research standards in this area. Three out of five studies reported adverse events such as hypersensitivity in the treated area (Eguaras et al., 2019), pain intensity increased for about 48h or even a longer time (De Marco et al., 2022) to full enteral feeding in infants (Haiden et al., 2015). As VO does cause adverse effects, while conveying no or little benefits, its risk/benefit balance does not seem to be positive.

Our findings do not support the use of VO in any musculoskeletal or non-musculoskeletal condition. Yet, at present, VO is widely used by osteopaths, chiropractors, and some physiotherapists. We question whether VO should continue to be used in clinical routine unless new robust evidence supporting its usefulness emerges.

This systematic review with meta-analysis has several limitations. First, even though our literature searches were thorough, we can never be absolutely sure that no relevant studies have been missed. Second, the inclusion of many diverse conditions in one review complicates the interpretation of the results and might weaken the strength of our conclusions. Third,

considerable heterogeneity exists across the included RCTs in terms of treatment duration and outcome variables. These factors might limit the validity of our quantitative syntheses.

CONCLUSION

The findings of this systematic review with meta-analysis revealed that VO generates no clinical benefits for any musculoskeletal or non-musculoskeletal conditions. The fact that the most reliable RCTs tended to generate negative findings casts further doubt on the effectiveness of VO. Since most clinical trials included in our review were deeply biased, firm conclusions seem problematic.

Table 1. Qualitative synthesis of the results.

	Participants		**Intervention**					**Outcome (tool)**	**Main results**
Author (year)	**Mean age (SD)**	**Diagnosis**	**VO group**	**Control group**	**Session duration**	**Frequency (sessions/week)**	**Total number of sessions**		
Musculoskeletal disorders									
Low back pain									
Tozzi et al. 2012	VO: 39.8 (7) CG: 37.6 (1)	NSLBP	VO (n=109)	Sham VO (n=31)	3-4 min	1	1	Pain (SF-MPQ) Kidney mobility (KMS)	↑Pain ↑Kidney mobility
Panagopoulos et al. 2014	NR	LBP	VO + PT (n=30)	Sham VO + PT (n=32)	40 min	1-2	12	Pain (NPRS) Disability (RMDQ) Function (PSFS)	ND ND ND
Tamer et al. 2017	VO: 39.8 (7) CG: 37.6 (1)	CNSLBP	VO + PT (n=20)	PT (n=19)	NR	2	10	Pain (VAS) Disability (ODI) QoL (SF-36)	ND ND ↑QoL subparameters (physical function, energy, total function score)
Villalta-Santos et al. 2018	VO: 41.5 (10.3) CG: 40.5 (12.1)	CLBP	VO + PT (n=10)	Sham VO + PT (n=10)	50 min	1	5	Pain (VAS) Lumbar ROM (Schober test) Disability (RMDQ) Function (PSFS)	ND ↑Lumbar ROM ND ↑Function
Lo Basso et al. 2021	VO: 47 (9.6) CG: 45.9 (11.4)	NSLBP	VO (n=10)	Sham VO (n=10)	15 min	1	1	Pain (VAS) Lumbar ROM (Schober test) Kidney mobility (KMS)	↑Pain ND ↑Kidney mobility
Altınbilek et al. 2023	VO: 46.9 (13.4)	CMLBP	VO + PT (n=40)	Sham VO + PT (n=39)	50min	2 VO/Sham VO 5PT	15	Pain (VAS) Disability (RMDQ) Depression (BDI)	↑Pain ↑Disability ↑Depression

	CG: 46.9 (15.0)								
Vilas Boas Fernandes et al. 2023	VO: 42.3 (10.5) CG: 45.6(10.0)	CNSLBP	VO (n=38)	Sham VO (n=38)	15m	1	6	Pain (NPRS) Disability (ODI) Trunk flexion (finger-to-floor) Fear-Avoidance (FABQ)	ND ↑Disability ND ND
Neck pain									
De Oliveira Silva et al. 2018	VO: 23.8 (6.2) CG: 27.0(9.9)	CNSNP	VO (n=14)	Sham VO (n=14)	10 min	1	1	Pain (NPRS) Cervical ROM Electromyography	ND ND ND
Urinary incontinence									
De Marco et al.2021	VO: 45.4 (15.4) CG: 53.9(12.9)	Urinary incontinence	VO + PT (n=27)	Sham VO + PT (n=25)	15m VO/Sham VO 45-60m PT	1 VO/Sham VO 4 PT	5 VO/Sham VO 20 PT	Symptoms (ICIQ-UI-SF) Vaginal resting pressure (manometry) MVC (manometry)	ND ND ND
Non-musculoskeletal conditions									
Irritable bowel syndrome									
Attali et al. 2013	50 (2)	IBS	VO (n=15)	Sham VO (n=16)	45 min	1	3	Constipation (VAS) Diarrhea (VAS) Abdominal distension (VAS) Abdominal pain (VAS) Rectal sensitivity Colonic transit time	ND ND ND ND ↑Rectal sensitivity ND
EL-Din Hammam et al.2022	VO: 38 CG: 38	IBS	VO (n=30)	Control (n=30)	15-30 min	2	12	Abdominal distension (VAS) Girth (cm) Depression (BDI)	↑Abdominal distension ↑Girth ↑Depression

								Anxiety (STAI)	↑Anxiety
Breast cancer									
Lagrange et al. 2019	VO: 57.2 (10.2) CG: 54.4 (12.1)	Breast cancer	VO (n=54)	Sham VO (n=40)	15 min	NR	3	QoL (EORTC QLQ-C30)	ND
Very low birth weight infants									
Haiden et al. 2015	VO: 26 (1) weeks CG: 28(2) weeks	Very low birth weight infants	VO (n=21)	Control (n=20)	60m	3	3	Meconium excretion (days) Feeding amount (ml/kg) Full enteral feedings (day of life) Duration of stay (days) Weight at discharge (gram)	ND ND ↓ Full enteral feedings ND ND
Gastroesophageal reflux									
Eguaras et al. 2019	VO: 48.1 (14.0) CG: 49.4(13.7)	Gastroesophageal reflux	VO (n=31)	Sham VO (n=29)	5 min	1	2	Symptoms (GERDQ) PPT (algometer) Cervical ROM	↑Symptoms ↑PPT ↑Cervical ROM
Polycystic ovarian syndrome									
Yosri et al. 2022	VO: 26.2(14.0) CG: 27.5(2.2)	Polycystic ovarian syndrome	VO + diet (n=15)	Diet (n=15)	NR	1 during the 1st month 1 each 2 weeks for 2 months	8	Symptoms (PCOSQ) Weight BMI	↑Symptoms ND ND

↑Statistically significant improvement. ↓ Statistically significant worsening. ND: no statistically significant differences.

VO: visceral osteopathy; CG: control group; NR: no reported; LBP: low back pain; NSLBP: non-specific low back pain; CNSLBP: chronic non-specific low back pain; CMLBP: chronic mechanical low back pain; CNSNP: chronic non-specific nek pain; IBS: irritable bowel syndrome; PT: physical therapy; VAS: visual analogue scale; NPRS: numeric pain rating score; SF-MPQ: McGill pain questionnaire; ROM: range of motion; ODI: Oswestry disability index; RMDQ: Roland Morris disability questionnaire; KMS: kidney mobility score; PSFS: patient specific functional scale; BDI: beck depression inventory; STAI: state-trait anxiety inventory; FABQ: fear avoidance believes questionnaire; ICIQ-UI-SF: international consultation on incontinence questionnaire short-form; MVC: maximum voluntary contraction; EORTC QLQ-C30: european organization for the research and treatment of cancer quality of life questionnaire; GERD-Q: gastro-esophageal reflux disease impact scale; PCOSQ: polycystic ovary syndrome quality of life scale.

Table 2. Synthesis of quantitative results and certainty of evidence.

Certainty assessment							Nº of patients		Effect		Certainty	
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[visceral]	[control]	Relative (95% CI)	Absolute (95% CI)		
Pain intensity												
7	RCTs	serious[a]	serious[c]	serious[e]	not serious	none	220	141	-	SMD **0.46 SD** (0.93 lower to 0.02 higher.)	⨁◯◯◯ Very low	
Disability												
4	RCTs	serious[a]	serious[c]	serious[e]	not serious	none	100	97	-	SMD **0.16 SD** (0.85 lower to 0.52 higher.)	⨁◯◯◯ Very low	
Range of motion												
4	RCTs	serious[a]	not serious	serious[e]	not serious	none	72	72	-	SMD **0.2 SD higher.** (0.15 lower to 0.55 higher.)	⨁⨁◯◯ Low	
Physical function												
3	RCTs	serious[a]	not serious	serious[e]	not serious	none	62	59	-	SMD **0.26 SD** (0.62 lower to 0.1 higher.)	⨁⨁◯◯ Low	
Kidney mobility												
2	RCTs	very serious[b]	very serious[d]	serious[e]	serious[f]	Publication bias suspected	119	41	-	MD **3.38 higher.** (2.13 lower to 8.89 higher.)	⨁◯◯◯ Very low	

MD: mean difference; SMD: standardized mean difference.

[a] Risk of bias was downgraded one level because more than 50% of the studies included presented high risk of bias.

[b] Risk of bias was downgraded two levels because more than 75% of the studies included presented high risk of bias.

[c] Inconsistency was downgraded one level because of the context of the results, the wide confidence intervals, and I^2 statistic (>50%).

[d] Inconsistency was downgraded two level because of the context of the results, the sample size heterogeneity, the wide confidence intervals, and the I^2 statistic (> 75%).

[e] Indirectness was downgraded because the interventions were heterogeneous.

[f] Imprecision was downgraded because the number of participants were not equally distributed.

Explanations:

High: We are very confident that the true effect is close to the estimate of the effect.

Moderate: We are moderately confidence in the effect estimate. The true effect is close to the estimate of the effect, but the result can be different.

Low: Confidence in the effect estimate is limited, the true effect can be substantially different from the estimate of the effect.

Very Low: There is little confidence in the effect estimate, the true effect is likely to be substantially different from the estimate effect.

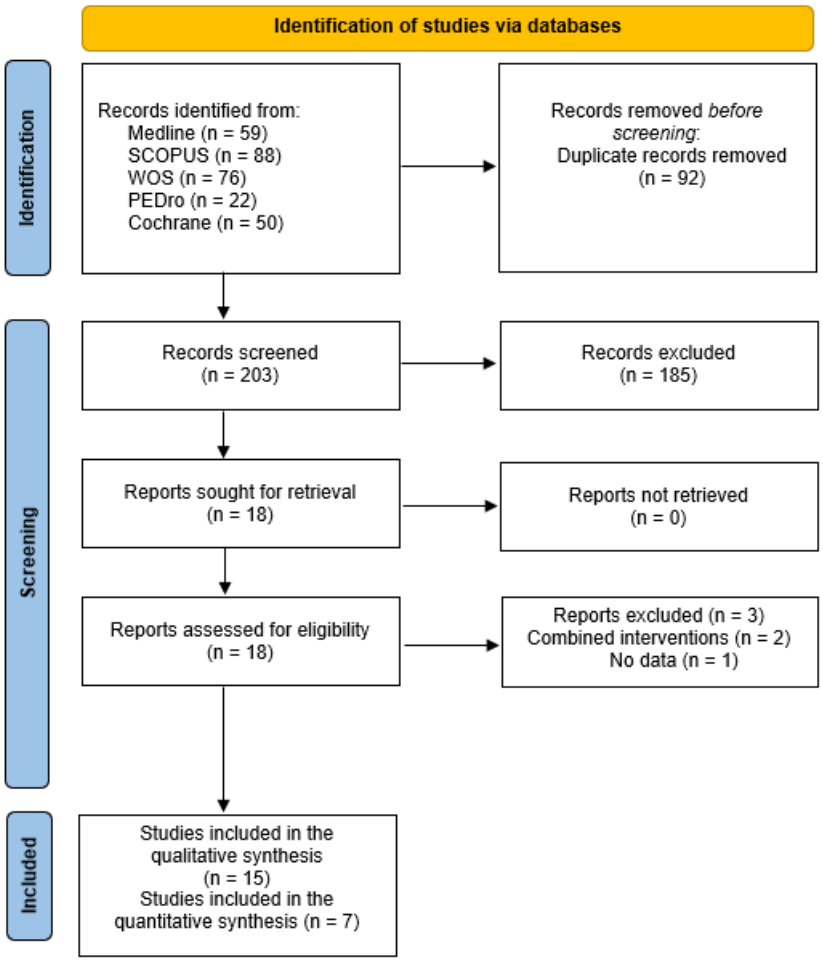

Figure 1. Flowchart diagram.

Figure 2. Cochrane RoB2 tool.

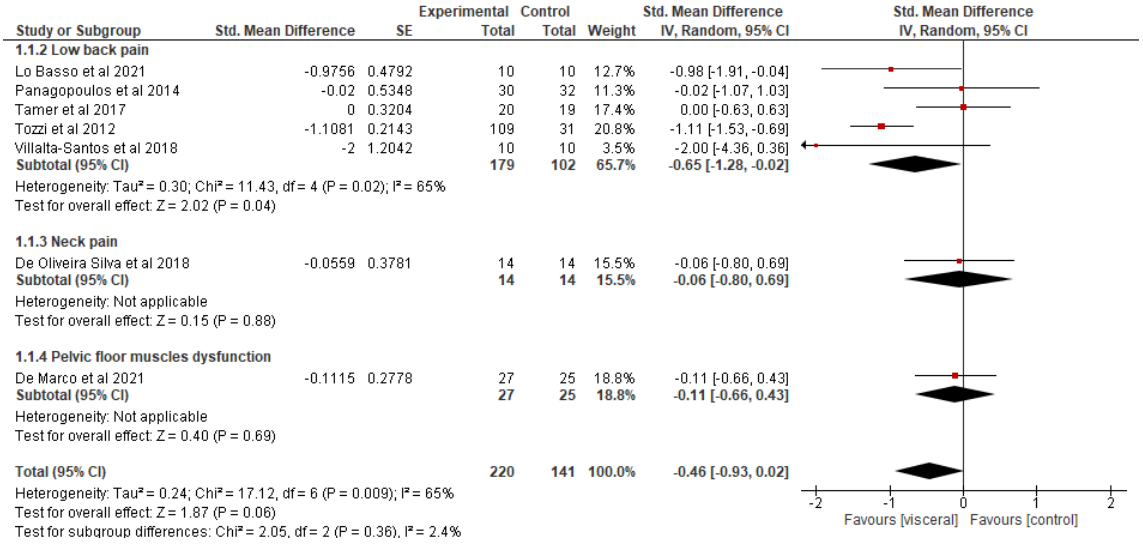

Figure 3A. Forest plot for pain intensity.

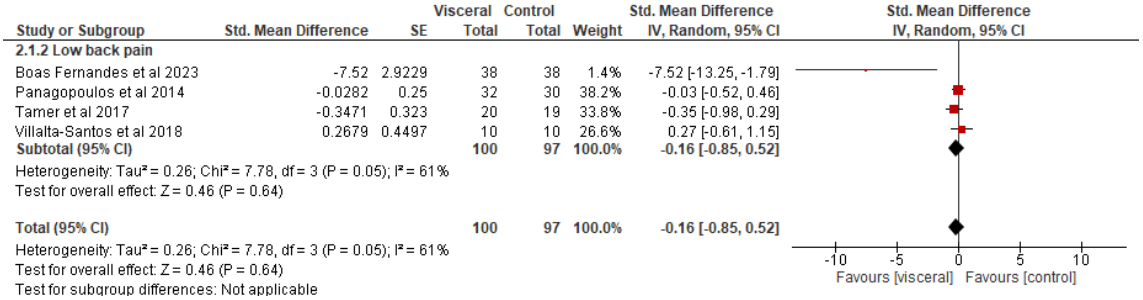

Figure 3B. Forest plot for disability.

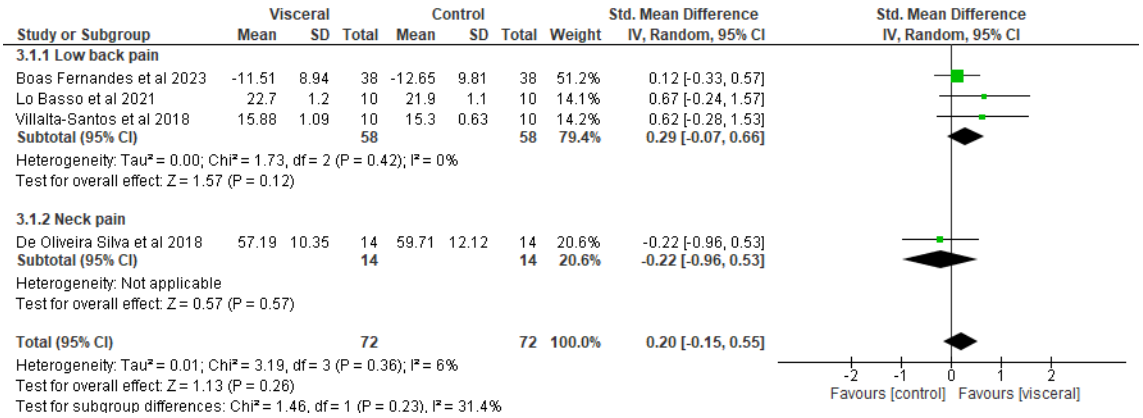

Figure 3C. Forest plot for flexion range of motion.

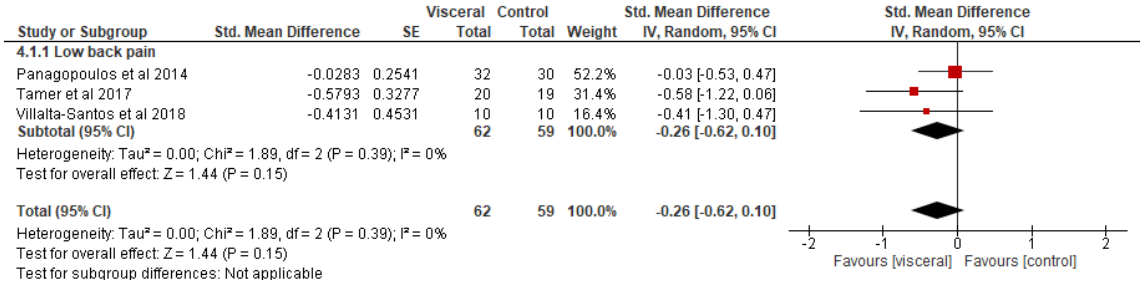

Figure 3D. Forest plot for physical function.

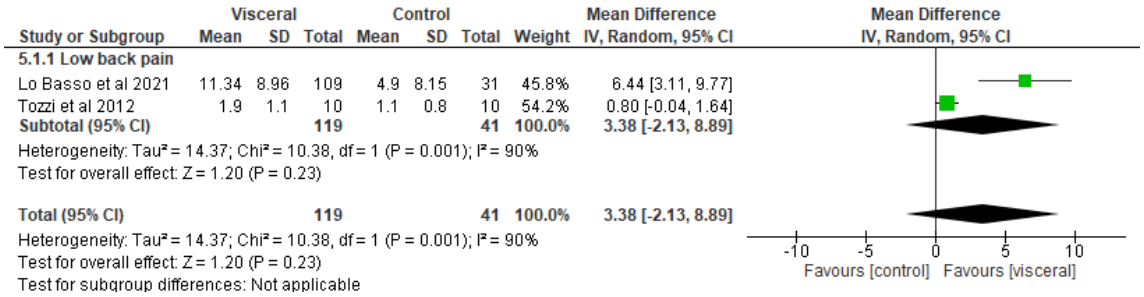

Figure 3E. Forest plot for kidney mobility.

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Systematic Review

Is Craniosacral Therapy Effective? A Systematic Review and Meta-Analysis

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Abstract: Objectives: The aim of this study was to evaluate the clinical effectiveness of craniosacral therapy (CST) in the management of any conditions. Methods: Two independent reviewers searched the PubMed, Physiotherapy Evidence Database, Cochrane Library, Web of Science, and Osteopathic Medicine Digital Library databases in August 2023, and extracted data from randomized controlled trials (RCT) evaluating the clinical effectiveness of CST. The PEDro scale and Cochrane Risk of Bias 2 tool were used to assess the potential risk of bias in the included studies. The certainty of the evidence of each outcome variable was determined using GRADEpro. Quantitative synthesis was carried out with RevMan 5.4 software using random effect models. Data Synthesis: Fifteen RCTs were included in the qualitative and seven in the quantitative synthesis. For musculoskeletal disorders, the qualitative and quantitative synthesis suggested that CST produces no statistically significant or clinically relevant changes in pain and/or disability/impact in patients with headache disorders, neck pain, low back pain, pelvic girdle pain, or fibromyalgia. For non-musculoskeletal disorders, the qualitative and quantitative synthesis showed that CST was not effective for managing infant colic, preterm infants, cerebral palsy, or visual function deficits. Conclusions: The qualitative and quantitative synthesis of the evidence suggest that CST produces no benefits in any of the musculoskeletal or non-musculoskeletal conditions assessed. Two RCTs suggested statistically significant benefits of CST in children. However, both studies are seriously flawed, and their findings are thus likely to be false positive.

Keywords: complementary therapies; osteopathy; systematic review; meta-analysis

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1. Introduction

Craniosacral therapy (CST) is defined as an intervention based on a gentle touch that allegedly releases restrictions in any tissues influencing the craniosacral system [1]. It has been considered as complementary and alternative medicine by the World Health Organization (WHO) and has been included in the Benchmarks for Osteopathic Education of the WHO [2].

Osteopathy is frequently used by patients with conditions such as back pain, neck pain, fibromyalgia, digestive disorders, or infantile colic [3–5]. International surveys have reported that 23% to 90% of osteopaths use CST. Specifically in Europe, between 70% and 89% of the interviewed osteopaths use CST always or often [4,6–9]; and 23% to 46% use it as a first-line treatment [10,11]. The relationship between the craniosacral system and the mentioned diseases has been theoretically based on implausible and unproven anatomical claims and connections [12], which means that no real relationship has been established, making the use of CST less than plausible.

The biological model of CST is commonly known as the "primary respiratory mechanism" (PRM) or "craniosacral mechanism". It assumes that the cranial structures present intrinsic mobility and can be detected by manual palpation [13]. These anatomical connections include minuscule or even nanoscopic motions of the osseous and membranous movements of the skull and its contents [14]. The underlying assumption is that movement in the cranial structures causes rhythmic movements of the cerebrospinal fluid from the cranium to the sacrum and specific changes in the dural membranes, as well as cranial and sacral bones [15]. To date, no evidence is available to suggest any mobility of the cranial bones. Under normal conditions, the cranial sutures fuse completely between the ages of 13 and 18 years, which means that adult cranial bones are fused [16,17]. In addition, the reliability of the palpation of the PRM is not supported by sound evidence. Guillaud et al. [18] reviewed nine studies testing the intra- and inter-rater reliability. All had a high risk of bias and failed to demonstrate that the palpation of the PRM is a valid diagnostic method.

Hestbaeck et al. [5] pointed out that despite the lack of benefits found in favor of CST in previous clinical trials and the low methodological quality presented in some of them, the use of osteopathy is supported by the interest of the patients in such therapies. However, the popularity of a therapy is a poor indicator of its effectiveness, and all interventions must demonstrate their true value through well-designed clinical trials.

The clinical effectiveness of CST has been tested in numerous clinical trials and summarized in several previous systematic reviews and meta-analyses. Three systematic reviews concluded that there was insufficient evidence to support the application of CST in patients with headache disorders, low back pain, lateral epicondylitis, fibromyalgia, visual alterations, asthma, attention deficit hyperactive disorders, infantile colic, preterm infants, and cerebral palsy mainly because the studies included were seriously flawed [1,15,18]. However, these systematic reviews also included studies not related to the clinical effectiveness of CST. Only Haller et al. [19] conducted a systematic review and meta-analysis suggesting that CST was effective in managing chronic pain in different musculoskeletal conditions. However, the combination of different conditions, such as fibromyalgia and neck pain, in the same forest plot decreases the validity of these results for combining populations that are not homogeneous.

Since the publication of these papers, several new randomized clinical trials (RCTs) of CST have emerged. The aim of this systematic review and meta-analysis is to evaluate the totality of the evidence for or against the clinical effectiveness of CST in the management of any conditions.

2. Materials and Methods

2.1. Study Design

A systematic review with meta-analysis was designed following the PRISMA statement and the Cochrane recommendations [20]. The protocol of this review was prospectively registered in PROSPERO (identification number CRD42023454524).

2.2. Search Strategy

The bibliographical searches were carried out in PubMed, the Physiotherapy Evidence Database (PEDro), Cochrane Library, Web of Science (WOS), and Osteopathic Medicine Digital Library (OSTMED) from inception to August 2023. Medical Subject Heading (MeSH) terms and grey terms were applied in the search strategy: osteopathic manipulation, osteopathic cranial manipulative medicine, cranial osteopathic manipulative medicine, cranial osteopathy, and craniosacral therapy, among others. The search strategy used in each database is shown in Appendix A. The reference lists of the included studies and the above-mentioned previous systematic reviews were hand-searched.

2.3. Eligibility Criteria and Study Selection

Studies were considered if they: included patients with musculoskeletal or non-musculoskeletal conditions; applied CST in isolation or in addition to standard care; compared the craniosacral intervention to a sham control or standard care intervention; reported variables related to the clinical effectiveness; and were designed as randomized controlled trials. Studies were excluded if they: included healthy participants; applied a multimodal intervention or comparator in which the effects of CST could not be extrapolated; reported no clinical outcomes (but only variables such as heart rate, skin conductance, or breathing rate), or the outcome measures were not quantified using validated instruments.

The reference lists retrieved from each database were exported to Mendeley to remove duplicates. Two authors (LC and AC) independently reviewed the title and abstract of each retrieved study to determine its potential eligibility. The studies that met the eligibility criteria were assessed in full text by the same authors. A third author (SJ) was consulted in case of discrepancies.

2.4. Data Extraction

The data extraction was performed independently by the two authors using a predetermined sheet adapted from the Cochrane Collaboration. The data extracted were the characteristics of the population (sex ratio, mean age, and diagnosis), type of interventions (session duration, sessions per week, and total number of sessions), outcome variables, and results. Data were analyzed using a qualitative and quantitative synthesis.

2.5. Methodological Quality, Risk of Bias, and Certainty of Evidence

The methodological quality, risk of bias, and certainty of evidence were assessed using the PEDro scale, Cochrane Risk of Bias 2 tool, and GRADEPro, respectively. The same authors independently performed the assessments.

The PEDro scale is an 11-item scale based on a Delphi list to assess the methodological quality of clinical trials [21]. A score of 7 or above was considered "high" quality, 5 to 6 was considered "fair" quality, and 4 or below was considered "poor quality". The first item of the PEDro scale (eligibility criteria) is related to external validity and was not considered in the total score.

The Risk of Bias 2 tool was used to determine the potential risk of bias in the RCTs and classified them as low, unclear, or high risk, based on five domains. The combination of the previously mentioned five items was used to determine the overall risk of bias rating for the entire study [22].

GRADEPro categorizes the certainty of evidence as "high", "moderate", "low", or "very low". A moderate or high certainty indicates that we are moderately or very confident in the effect estimate. A low certainty means that the true effect can be substantially different from the estimated one, and very low certainty means that the true effect is likely to be substantially different from the estimated effect.

The certainty of evidence for the meta-analysis was downgraded based on the presence of certain factors, including the risk of bias, inconsistency of the results, indirectness of evidence, and imprecision. The risk of bias was downgraded by one level or two levels when 25% or 50% of the subjects included in a study originated from clinical trials with a high risk of bias: lack of random allocation and/or sample size calculation of participants, allocation concealment, and/or personnel blinding of outcome assessors. Inconsistency of results was downgraded by one or two levels when the I^2 was $\geq$50 or $\geq$75 [23]. Indirectness of evidence was downgraded by one level if different populations, interventions, or comparators were included, and imprecision was downgraded by one or two levels if the number of participants in the comparison was less than 100 or $\leq$30 individuals [24].

2.6. Data Synthesis and Analysis

A qualitative synthesis of the results was conducted and, whenever this was possible, a quantitative synthesis (meta-analysis) was carried out using the RevMan 5.4 software.

Meta-analyses were performed if at least two studies were sufficiently homogeneous. Studies were considered homogeneous if they applied a common intervention, measured a common outcome, and included the same population. When a three-arm study was included, the data from the repeated groups were divided to avoid duplicate data [25]. Outcomes were analyzed based on the post-intervention means and standard deviations (SDs) by calculating the mean difference (MD) when RCTs used the same scale, or standardized mean difference (SMD) when they used different scales, with 95% coefficient intervals (CIs). SMD classifies the effects estimates as small (SMD at least 0.2 but less than 0.5), medium (SMD from 0.5 to less than 0.8), or large (SMD 0.8 or greater) [26]. Significance was set at a p-value < 0.05.

A random-effect meta-analysis was performed when combinations of intervention effects were based on the assumption that the studies are not all estimating the same intervention effect [27].

To detect publication bias, Begg and Egger tests were conducted using EPIDAT 3.1. Funnel plots were not reported because fewer than 10 trials were available.

3. Results

The searches yielded 1511 papers of which 21 RCTs were selected for full-text review. Three studies were excluded for not presenting a control, sham, or standard care group [28–30], two studies used multi-interventions from which the effects of CST could not be extrapolated [31,32], and one did not measure outcome variables evaluating the clinical effectiveness of CST [33]. Fifteen RCTs were thus included in the qualitative synthesis and seven were submitted for the quantitative synthesis. The description of the selection process is shown in the PRISMA flowchart diagram (Figure 1).

Regarding the methodological quality of the studies evaluated with the PEDro scale, three studies were classified as low quality [34–36], eight studies as fair quality [37–44], and four as high quality [19,33,45,46] (Table 1).

The overall risk of bias was considered to be high for eight studies [34–37,39–41,43]. In the risk of bias tool, eight studies showed an unclear randomization process [34,36–39,41,43,46], and almost all the studies presented concerns about the measurement of the outcome variables [34–45,47] and about the selection of the reported results [34–37,39–41,43–48]. Figure 2 shows in detail the Cochrane Risk of Bias 2 tool results.

3.1. Clinical Effectiveness on Musculoskeletal Conditions

Eight RCTs were included, evaluating the clinical effectiveness of CST in patients with musculoskeletal conditions such as headache disorders, neck pain, low back pain, pelvic girdle pain, and fibromyalgia. Seven of them assessed pain intensity, and six assessed disability or impact.

In the qualitative synthesis, six out of the seven studies assessing pain intensity reported statistically significant improvements in favor of the CST group [34,35,38,39,47,48]. Comparing the qualitative results to the minimum clinically important changes (MCID) described for each condition, none of the changes achieved were superior to the MCID described for headache disorders (2.5) [49], neck pain (2.1) [50], low back pain (1.5) [51], pelvic girdle pain (1.3) [52], or fibromyalgia (2.3) [53] (Table 1). Three out of the six studies assessing disability or impact reported statistically significant improvements in favor of the CST group [34,38,47]. Comparing the qualitative results to the MCIDs, the change achieved in headache impact was not superior to the MCID stated (5.5–8) [54,55]. Only Haller et al. [47] reported a change in the Neck Disability Index higher than the MCID (7) [56] (Table 1).

In the quantitative synthesis, the certainty of evidence was very low on pain intensity (Appendix B). The meta-analysis provided a statistically significant but clin-

ically insignificant difference in pain intensity in patients with headache disorders (mean difference (MD) −0.79 95% CI: −1.39 to −0.20, I^2 92%), and no benefits to low back pain (standardized mean difference (SMD) −1.68 95% CI: −3.89 to 0.52, I^2 93%) (Supplementary Figure). The certainty of the evidence was very low on headache impact (Appendix B), with no statistically significant effects for CST (SMD 0.02 95% CI: −0.44 to 0.48, I^2 93%) (Supplementary Figure).

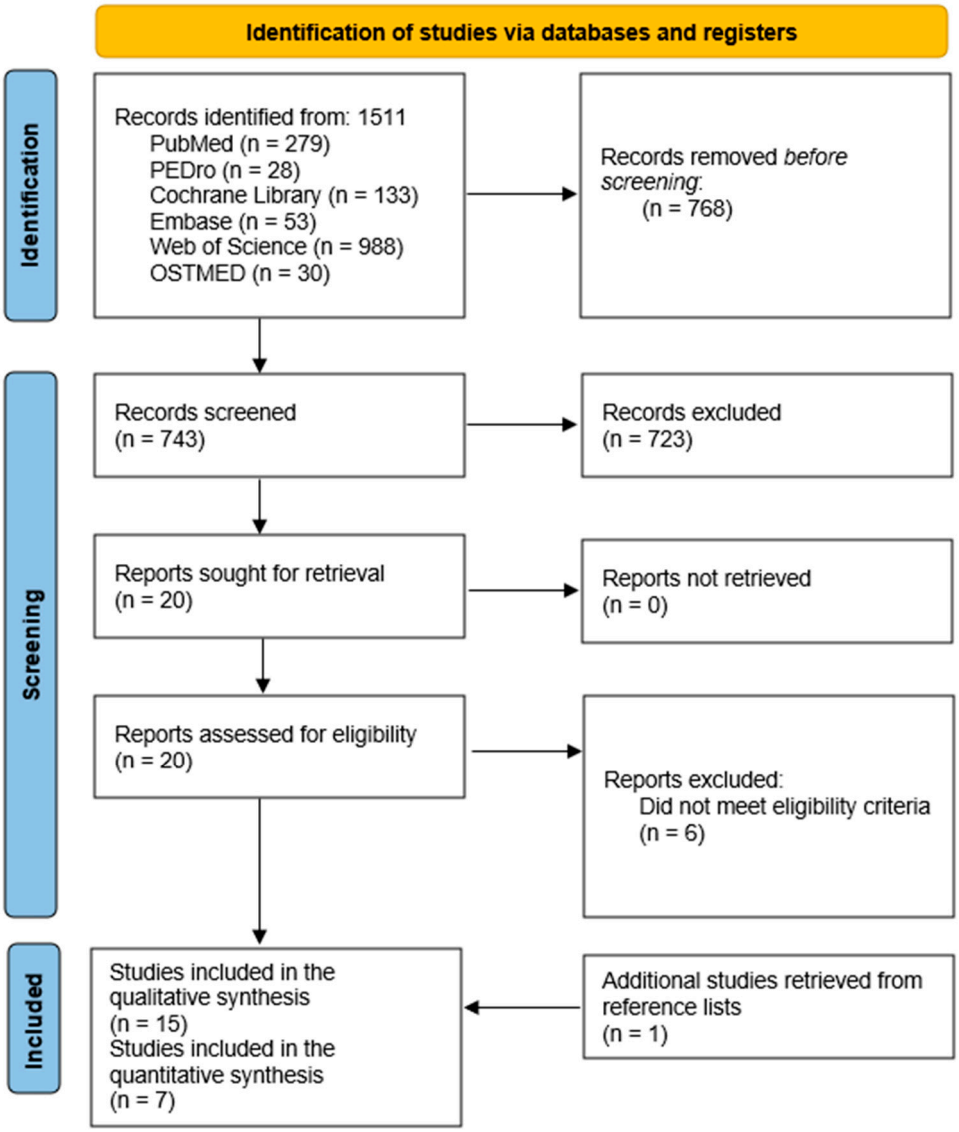

Figure 1. Flowchart diagram.

Table 1. Qualitative synthesis of the results.

Participants			Intervention					Outcome (Tool)		Main Results	PEDro Score
Author (Year)	**Mean Age (SD)**	**Diagnosis**	**CST Group**	**Control Group**	**Session Duration**	**Frequency (Sessions/Week)**	**Total Number of Sessions**				
Musculoskeletal disorders Headache disorders											
Hanten et al., 1999 A [34]	36 (12)	TTH	CST (n = 20)	Resting position (n = 20)	10 m	1 s/w	1	– –	Pain (VAS) Impact (VAS)	ND ND	4
Hanten et al., 1999 B [34]	36 (12)	TTH	CST (n = 20)	Control (n = 20)	10 m	1 s/w	1	– –	Pain (VAS) Impact (VAS)	↑ Pain ↑ Impact	4
Arnadottir et al., 2013 [37]	37.6 (9.3)	Migraine	CST (n = 10)	Control (n = 10)	NR	1.5 s/w	6	–	Impact (HIT-6)	ND	5
Muñoz-Gómez et al., 2022 [38]	CST: 40.92 (7.95) CG: 37.64 (9.42)	Migraine	CST (n = 25)	Sham intervention (n = 25)	45 m	1 s/w	8	– –	Pain (VAS) Migraine severity (HDI)	↑ Pain ↑ Severity	6
Neck pain											
Haller et al., 2016 [47]	CST: 44.2 (9.7) CG: 45.0 (10.5)	CNP	CST (n = 27)	Sham intervention (n = 27)	45 m	1 s/w	8	– –	Pain (VAS) Neck disability (NDI)	↑ Pain ↑ Disability	8
Low back pain											
Castro-Sánchez et al., 2011 [33]	CST: 50 (11) CG: 53 (9)	CLBP	CST (n = 32)	Control (n = 32)	50 m	1 s/w	10	– –	Pain (VAS) Disability (RMQ and ODI)	↑ Pain ND	7
Mazreati et al., 2021 [39]	CST: 34.28 (3.28) CG: 33.11 (3.20)	CLBP	CST (n = 30)	Control (n = 29)	30–45 m	NR	8	–	Pain (McGill questionnaire)	↑ Pain	6

Table 1. *Cont.*

Participants			Intervention					Outcome (Tool)		Main Results	PEDro Score
Author (Year)	**Mean Age (SD)**	**Diagnosis**	**CST Group**	**Control Group**	**Session Duration**	**Frequency (Sessions/Week)**	**Total Number of Sessions**				
					Pelvic girdle pain						
Elden et al., 2013 [45]	CST: 30.6 (3.9) CG: 31.3 (4.3)	Pregnant women with pelvic girdle pain	CST + standard care (n = 55)	Standard care (n = 57)	45 m	1 s/w	3	– – – –	Morning pain (VAS) Evening pain (VAS) Discomfort of pain (VAS) Disability (DRI)	↑ Morning pain ND ND ND	8
					Fibromyalgia						
Matarán-Peñarrocha et al., 2011 [35]	CST: 48.25 (13.34) CG: 52.26 (10.98)	Fibromyalgia	CST (n = 43)	Sham intervention (n = 41)	60 m	2 s/w	50	–	Pain (VAS)	↑ Pain	4
					Non-musculoskeletal conditions Infantile colic						
Castejón-Castejón et al., 2022 [40]	CST: 39.14 (20.15) days CG: 33.69 (15.14) days	Infantile colic	CST (n = 29)	Control (n = 25)	30–40 m	1 s/w	1 to 3	– –	Crying diary Sleeping diary	↑ Crying ↑ Sleeping	6
Hayden et al., 2006 [41]	CST:46.4 (5.4) days CG: 44.5 (5.0) days	Infantile colic	CST (n = 14)	Control (n = 14)	30 m	1 s/w	4	– –	Crying diary Sleeping diary	↑ Crying ↑ Sleeping	5
					Preterm infants						
Raith et al., 2016 [42]	CST: 28 (25–33) weeks CG: 30 (27–33) weeks	Preterm infants	CST (n = 12)	Control (n = 13)	NR	2 s/w	6	–	Motor Function (GMA, GMOS)	ND	5
					Autism						
Mishra and Senapati 2015 [43]	CST: 3–10 CG: 3–10	Children with autism	CST + standard care (n = 10)	Standard care (n = 10)	60 m	5 s/w	40	–	Autism evaluation (ATEC)	↑ Autism evaluation	5

Table 1. *Cont.*

Participants			Intervention					Outcome (Tool)	Main Results	PEDro Score
Author (Year)	**Mean Age (SD)**	**Diagnosis**	**CST Group**	**Control Group**	**Session Duration**	**Frequency (Sessions/Week)**	**Total Number of Sessions**			
Hyperactivity disorder										
Amrovabady et al., 2013 [36]	CST: 9.5 CG: 9.9	Attention deficit hyperactivity disorder	CST + standard care (n = 12)	Standard care (n = 12)	30 m	2 s/w	15	– Symptoms (CSI-4) – Behaviour (CPRS)	↑ Symptoms ↑ Behaviour	3
Cerebral palsy										
Wyatt et al., 2011 [44]	CST: 8.0 (5–12) CG: 7.6 (5–12)	Cerebral palsy	CST (n = 62)	Control (n = 67)	NR	1 s/month	6	– Motor function (GMFM66) – Physical function (CHQ) – Pain (PPP)	ND ND ND	6
Visual function										
Sandhouse et al., 2010 [46]	24.38 (3.03)	Patients with myopia, hyperopia, or astigmatism	CST (n = 15)	Sham intervention (n = 14)	5 m	1 s/w	1	– Distance visual acuity testing – Accomodative system testing – Local stereoacuity testing – Pupillary size testing – Retinoscopy – Vergence system testing	ND ND ND ↑ right pupillary size ND ND	7

↑ Statistically significant improvement. CST: craniosacral; CG: control group; TTH: tension-type headache; CNP: chronic neck pain; CLBP: chronic low back pain; NR: no reported; VAS: Visual Analog Scale; HIT-6: Headache Impact Test; HDI: Headache Disability Index; NDI: Neck Disability Index; RMQ: Roland Morris Questionnaire; ODI: Oswestry Disability Index; DRI: Disability Rating Index; GMA: General Movement Assessment; GMOS: General Movement Optimality Score; ATEC: Autism Treatment Evaluation Checklist; CSI-4: Children Severity Index; CPRS: Conners' Parent Rating Scale; GMFM-66: Gross Motor Function Measure; CHQ: Child Health Questionnaire; PPP: Pediatric Pain Profile; ND: no difference.

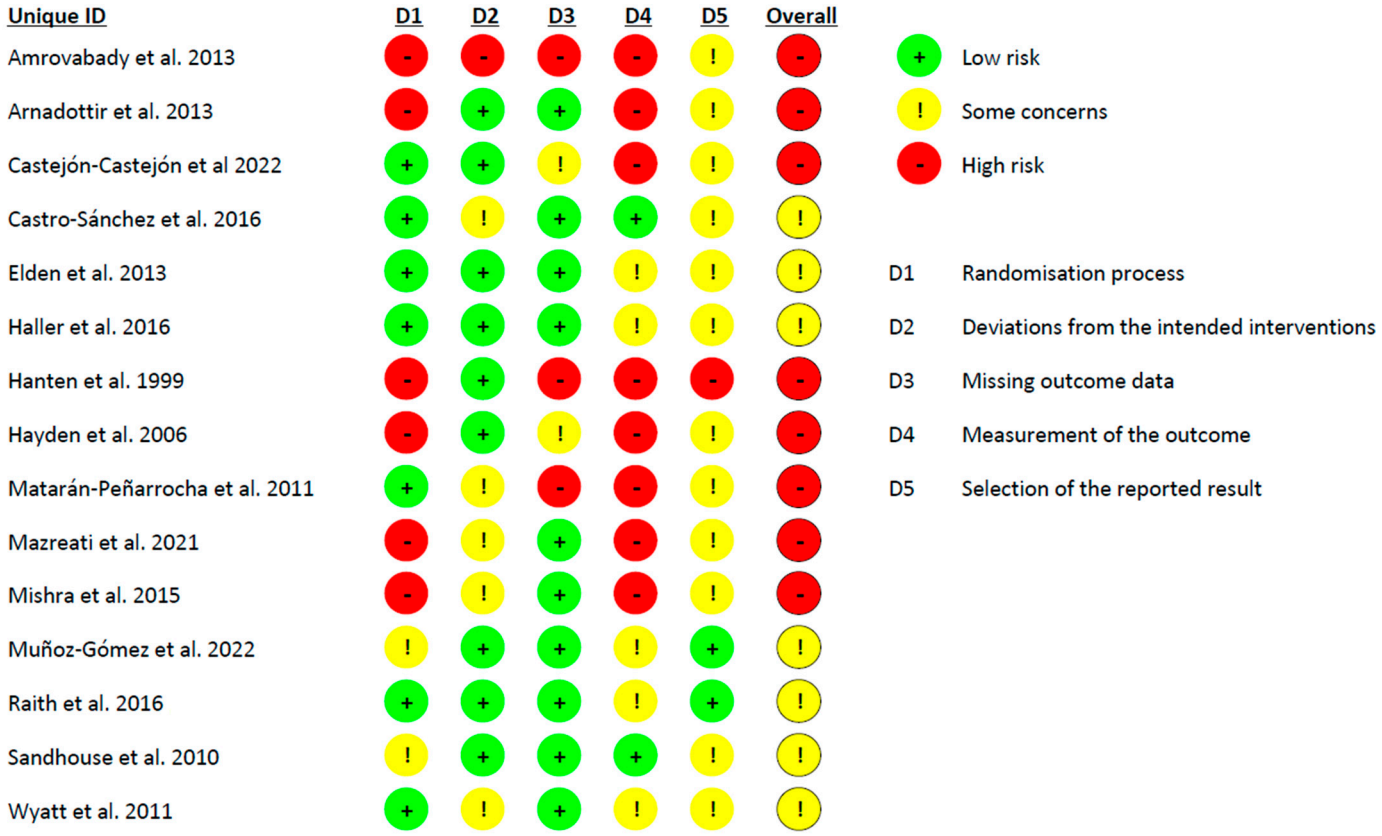

Figure 2. Cochrane Risk of Bias 2 tool [33–47].

3.2. Clinical Effectiveness for Non-Musculoskeletal Conditions

Seven studies evaluated the clinical effectiveness of CST in children with infantile colic, autism, attention deficit hyperactivity disorder, cerebral palsy, preterm infants, and patients with visual function deficits.

In the qualitative synthesis, no statistically significant improvements were reported in patients with cerebral palsy, preterm infants, or patients with visual function deficits [42,44,46]. Four out of the seven studies reported statistically significant improvements in favor of the CST groups in children with infantile colic [40,41], autism [43], and deficit hyperactivity disorder [36] (Table 1). No MCIDs were found for the outcome variables assessed.

In the quantitative synthesis, the certainty of the evidence was very low in terms of crying and sleeping time of children with infantile colic (Appendix B). The meta-analysis showed no statistically significant results for crying time (MD −1.78 95% CI: −4.01 to 0.44, I^2 98%) and sleeping time (MD 1.77 95% CI: −0.12 to 3.66, I^2 90%) in infantile colic (Supplementary Figure).

3.3. High- Versus Low-Quality Studies

In general, the studies that had a lower risk of bias and higher scores on the PEDro scale showed no statistically significant differences between CST and control interventions. In contrast, the studies with higher risk of bias and lower PEDro scores suggested statistically significant differences in favor of CST. In musculoskeletal and non-musculoskeletal conditions, all the studies that had a PEDro score ≤ 6 and a high risk of bias showed statistically significant benefits in favor of CST. Studies with PEDro scores ≥ 6 and low risk of bias showed no benefits favoring CST.

Only the outcome measure of pain intensity in RCTs of musculoskeletal conditions showed different results; those with a PEDro score ≤ 7 and high risk of bias generated positive but clinically insignificant changes in pain intensity in the CST groups. The only

study that was an exception, scoring 8 points in the PEDro score and yielding a positive result, was the one by Haller et al.

3.4. Adverse Events

Ten RCTs failed to mention adverse events. Five RCTs assessed adverse events, and all of them reported no serious adverse events [35,38,40,44,45].

4. Discussion

Our systematic review and meta-analysis were aimed at determining whether CST is clinically effective for musculoskeletal or non-musculoskeletal disorders. Fifteen RCTs were included in the qualitative and seven in the meta-analyses. For musculoskeletal disorders, the qualitative and quantitative synthesis suggested that CST produces no statistically significant or clinically relevant changes in pain and/or disability/impact in patients with headache disorders, neck pain, low back pain, pelvic girdle pain, or fibromyalgia. For non-musculoskeletal disorders, the qualitative and quantitative synthesis showed that CST was not effective in managing infant colic, preterm infants, cerebral palsy, or visual function deficits.

Several previous systematic reviews have investigated the effects of CST in different populations [1,15,18,19,57–60]. Most of them concluded that there was insufficient evidence to support CST in any condition. Our findings are thus in accordance with the previously published evidence [1,15,18,57,60]. Our systematic review and meta-analysis is the first that critically evaluates all the currently available evidence on CST in musculoskeletal and non-musculoskeletal conditions.

4.1. Musculoskeletal Conditions

In musculoskeletal conditions, despite the fact that most of the included studies showed statistically significant improvements in favor of the CST, the qualitative and quantitative syntheses showed that CST did not produce relevant clinical effects. Only Haller et al. reported clinically relevant changes in patients with neck pain.

The validity of the results reported by some of the authors reporting positive results is, however, questionable. The studies that found statistically significant benefits in CST were not prospectively registered in any database [33,34,48], did not perform a concealed allocation [33,34,38], and did not use an intent-to-treat analysis, despite the fact that some of them presented a dropout rate higher than 15% [35,38,47,48]. Moreover, most of the studies were designed as single- or double-blind clinical trials, but all of them used a sham intervention without assessing the effectiveness of blinding. Finally, several studies assessed self-reported subjective outcome variables, which are open to reporting biases [33,34,38,48].

Haller et al. [47] reported clinically relevant changes and a PEDro score of 8; these findings should be interpreted with caution because of the limitations of this study: the study protocol was not prospectively registered. The authors described the method of patient blinding, but the success of the procedure was not evaluated. Furthermore, most of the outcome variables were self-reported, which carries a high risk of bias. In addition, there is a lack of clarity regarding patient assessments, the intervention, and the possibility of verbal and non-verbal interactions between the therapists that might impact the observed outcomes.

4.2. Non-Musculoskeletal Conditions

In non-musculoskeletal conditions, CST was not effective for children with cerebral palsy and patients with visual function deficits. Two RCTs found statistically significant differences in favor of CST for infantile colic. However, in both studies, the parents were unblinded and were asked to fill in the diaries regarding crying and sleeping times. In addition, approximately 14% of the infants assigned to the control group were lost to follow-up, yet no intent-to-treat analysis was conducted [40,41]. Furthermore, the results

of the quantitative synthesis showed no significant benefits, which is in accordance with previous systematic reviews and meta-analyses [60,61].

Two studies found statistically significant benefits of CST for children with autism and hyperactivity disorder [36,43]. However, no MCIDs were found to compare the results, and meta-analyses could not be performed because only one study was included for each condition. Neither study had prospectively registered the study protocol, randomized the participants correctly, and blinded the patients or the examiners. In addition, both studies used a small sample size. In the study by Mishra et al. [43], the parents received explanations about the benefits of CST; they then filled in the questionnaires, and no details were provided as to how the data were statistically analyzed. Therefore, these studies scored the lowest values in PEDro scores for non-musculoskeletal conditions.

Generally speaking, the RCTs of non-musculoskeletal conditions had multiple methodological flaws. All the studies that found positive effects of CST were conducted in children. Parents want to help their children and tend to opt for CST after other interventions fail [3]. In these studies, they were asked to record the outcome variables without being blinded, which inevitably introduces bias. The RCTs by Wyatt et al. [44] and Raith et al. [42] were the only studies that described assessor blinding, and these trials both found no statistically significant effects of CST.

Ten RCTs failed to mention adverse effects. Arguably, not reporting adverse effects in clinical trials constitutes a violation of research ethics [62]. The fact that the majority of trials completely neglected adverse effects can be seen as a reflection of the overall poor standards of research in this area.

4.3. Implications for Clinical Practice

From a clinical perspective, CST is an intervention widely used by osteopaths, chiropractors, and some physiotherapists. It is included in the benchmarks for training in osteopathy. Yet in our evaluation of its clinical effectiveness, no good evidence supports its use in any condition. Our findings are in accordance with several previous systematic reviews [1,15,18]. In our view, this suggests that CST is not an evidence-based therapy. Therefore, it should not be used in clinical routine unless new robust evidence supporting its usefulness emerges.

4.4. Limitations and Future Considerations

This systematic review and meta-analysis have several limitations. First, even though our literature searches were thorough, we can never be absolutely sure that no relevant studies have been missed. Second, the inclusion of many diverse conditions in one review complicates the interpretation of the results and might weaken the strength of our conclusions. Third, considerable heterogeneity exists across the included RCTs in terms of treatment duration and outcome variables. These factors might limit the validity of our quantitative syntheses.

5. Conclusions

Our evaluation fails to show CST to be clinically effective for musculoskeletal or non-musculoskeletal disorders. Two RCTs suggested statistically significant benefits of CST in children. However, both studies are seriously flawed, and their findings are thus likely to be false positive. To date, no sound evidence supports the use of CST for any condition. Considering the biological implausibility of the concepts of CST, we feel that future studies in this area may not be warranted. If further research is nonetheless initiated, it should be conducted with improved methodological quality by registering the protocol prospectively, performing an adequate random allocation, ensuring participants and examiners are blinded, and including objective outcome measures.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/healthcare12060679/s1, Supplementary Figure: Forest plot of the outcome variables.

Author Contributions: Conceptualization, E.E. and L.C.-L.; methodology, E.E. and L.C.-L.; software, L.C.-L. and S.J.-d.-B.; formal analysis, L.C.-L. and S.J.-d.-B.; resources, L.C.-L. and S.J.-d.-B.; data curation, L.C.-L., S.C.-B., J.E.-P. and A.C.-U.; writing—original draft preparation, L.C.-L., S.J.-d.-B., S.C.-B., J.E.-P. and A.C.-U.; writing—review and editing, E.E.; visualization, L.C.-L., S.J.-d.-B., S.C.-B., J.E.-P. and A.C.-U.; supervision, E.E.; project administration, L.C.-L. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A. Detailed Search Strategy According to the PRISMA Model

PUBMED
Search strategy: ("osteopathic manipulation" [MeSH] OR "cranial mobilization" OR "craniosacral mobilization" OR "craniosacral manipulation" OR "cranial therapy" OR "craniosacral" OR "osteopathic cranial manipulative medicine" OR "cranial osteopathy" OR "craniosacral osteopathy" OR "cranial manipulation" OR "cranial field" OR "cranial osteopathic manipulative medicine" OR "osteopathic cranial manipulative medicine" OR "cranial manipulative medicine" OR "primary respiratory mechanism" OR "cranial rhythmic impulse" OR "fourth ventricular") Filter: clinical trial/randomized controlled trial Data: 17 August 2023 Studies retrieved: 279
PEDRO Search strategy: craniosacral Data: 17 August 2023 Studies retrieved: 21 Search strategy: cranial osteopathy Data: 17 August 2023 Studies retrieved: 7
Cochrane Library Search strategy: ("osteopathic manipulation" OR "cranial mobilization" OR "craniosacral mobilization" OR "craniosacral manipulation" OR "cranial therapy" OR "craniosacral OR "osteopathic cranial manipulative medicine" OR "cranial osteopathy" OR "craniosacral osteopathy" OR "cranial manipulation" OR "cranial field" OR "cranial osteopathic manipulative medicine" OR "osteopathic cranial manipulative medicine" OR "cranial manipulative medicine" OR "primary respiratory mechanism" OR "cranial rhythmic impulse" OR "fourth ventricular") Data: 17 August 2023 Studies retrieved: 133
WOS Search strategy: "osteopathic manipulation " OR "cranial mobilization" OR "craniosacral mobilization" OR "craniosacral manipulation" OR "cranial therapy" OR "craniosacral" OR "osteopathic cranial manipulative medicine" OR "cranial osteopathy" OR "craniosacral osteopathy" OR "cranial manipulation" OR "cranial field" OR "cranial osteopathic manipulative medicine" OR "osteopathic cranial manipulative medicine" OR "cranial manipulative medicine" OR "primary respiratory mechanism" OR "cranial rhythmic impulse" OR "fourth ventricular" Data: 17 August 2023 Studies retrieved: 988
OSTMED Search strategy: "craniosacral therapy" OR "cranial osteopathy" OR "osteopathy in the cranial field" OR "osteopathic cranial manipulative medicine" Data: 17 August 2023 Studies retrieved: 30

Appendix B. Synthesis of Quantitative Results and Certainty of Evidence

Outcome	No. of Studies (Participants)	Risk of Bias	Inconsistency	Imprecision	Indirectness	Publication Bias	Pooled Effect Estimate	Certainty of Evidence
				Headache disorders				
Pain intensity	2 (110)	Very serious [a]	None	Serious [c]	None	Begg test: 0.29 Egger test: 0.01	MD: −0.79 (−1.39, −0.20)	Very low
Headache impact	2 (60)	Very serious [a]	None	Serious [c]	Serious [d]	No suspected	SMD: 0.02 (−0.44, 0.48)	Very low
				Low back pain				
Pain intensity	2 (123)	Very serious [a]	Very serious [b]	Serious [c]	None	No suspected	SMD: −1.68 (−3.89, 0.52)	Very low
				Infant colic				
Crying time	2 (82)	Very serious [a]	Very serious [b]	Serious [c]	Serious [d]	No suspected	MD: −1.78 (−4.01, 0.44)	Very low
Sleeping time	2 (82)	Very serious [a]	Very serious [b]	Serious [c]	Serious [d]	No suspected	MD: 1.77 (−0.12, 3.66)	Very low

MD: mean difference; SMD: standardized mean difference. [a] Risk of bias was downgraded because more than 50% of the studies included presented fair or low methodological quality. [b] Inconsistency was downgraded because I^2 was higher than 75%. [c] Imprecision was downgraded because the interventions were heterogeneous. [d] Indirectness was downgraded because the number of patients was <100.

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Review

"The Dark Side of Musculoskeletal Care": Why Do Ineffective Techniques Seem to Work? A Comprehensive Review of Complementary and Alternative Therapies

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Abstract: The increasing interest in complementary and alternative medicines (CAMs) for musculoskeletal care has sparked significant debate, particularly regarding their biological plausibility and clinical effectiveness. This comprehensive review critically examines the use of two of the most widely utilized CAMs—osteopathy and chiropractic care—over the past 25 years, focusing on their biological plausibility, clinical effectiveness, and potential mechanisms of action. Our analysis of current research and clinical studies reveals that osteopathy and chiropractic are based on concepts such as "somatic dysfunction" and "vertebral subluxation", which lack robust empirical validation. While these therapies are often presented as credible treatment options, studies evaluating their effectiveness frequently exhibit serious methodological flaws, providing insufficient empirical support for their recommendation as first-line treatments for musculoskeletal conditions. The effects and mechanisms underlying osteopathy and chiropractic remain poorly understood. However, placebo responses—mediated by the interaction of contextual, psychological, and non-specific factors—appear to play a significant role in observed outcomes. The integration of therapies with limited biological plausibility, whose effects may primarily rely on placebo effects, into healthcare systems raises important ethical dilemmas. This review highlights the need for rigorous adherence to scientific principles and calls for a more comprehensive investigation into biobehavioral, contextual, and psychosocial factors that interact with the specific effects of these interventions. Such efforts are essential to advancing our understanding of CAMs, enhancing clinical decision-making, promoting ethical practices, and guiding future research aimed at improving patient care in musculoskeletal disorders.

Keywords: complementary therapies; musculoskeletal diseases; biological plausibility; placebo effect; evidence-based medicine; osteopathic medicine; chiropractic

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1. Introduction

Musculoskeletal care as a health discipline has seen significant advancements in recent years, largely driven by the adoption of evidence-based approaches. However, a concerning phenomenon persists: the continued use of therapies within musculoskeletal care that lack empirical support and even biological plausibility. In this sense, the use of complementary and alternative medicines (CAMs) has shown an increase in various regions worldwide, with notable variations. For instance, in Europe, their use has risen from 26% to 40% in recent years, with countries such as Germany and Denmark leading these statistics [1,2] . Similarly, in the United States, a comparable increase has been observed [3,4]. On the other hand, in Asia, CAMs enjoy significant social and institutional acceptance, which fosters an even greater inclination toward their use, particularly in countries such as China, the Philippines, and South Korea [5].

Despite efforts by part of the healthcare community to promote evidence-based practices, the previous statistics showed that contemporary musculoskeletal care remains influenced by the historical adoption of CAMs that lack scientific backing. This phenomenon has gained traction despite the lack of empirical evidence due to the growing demand from patients for more integrative and holistic approaches, often as a response to dissatisfaction with conventional medicine and its associated adverse effects [6,7]. However, the popularity of a therapy is a poor indicator of its effectiveness, and interventions must demonstrate their true value through methodologically rigorous studies.

The most described negative experiences with conventional medicine range from unfavorable interactions between professionals and patients to perceptions of inefficacy and the side effects of traditional treatments [8]. However, the rejection of conventional medicine or poor perception of healthcare systems are not the only factors driving the use of CAMs. On the contrary, users of these therapies often are proactive individuals who choose their own treatments, seeking approaches they consider most effective [9]. Additionally, many of these practices, seemingly grounded in science, are used by healthcare professionals, which can generate greater confidence in their adoption by the public [8].

To illustrate this situation, consider pharmacological treatments for headaches, which are typically the first line of intervention for patients [10,11]. However, these medications are not without risks, and approximately one-third of headache patients report dissatisfaction with the results [12]. Consequently, many turn to CAMs, such as chiropractic care [13,14] or osteopathy [15].

CAMs are defined as "a diverse set of medical and healthcare systems, practices, and products that are not currently considered part of conventional medicine" [16]. They are characterized by a limited number of clinical trials supporting their hypotheses or testing methods to evaluate their results in diverse conditions, as they were originally considered outside of evidence-based practices. However, this situation has evolved, and numerous journals specializing in complementary and alternative therapies have been established and categorized within the Journal Citation Reports of the Web of Science database under Integrative and Complementary Medicine [17].

A clear distinction between complementary and alternative interventions must be pointed out. Complementary therapies, on the one hand, accept various models of disease and are open to being used alongside evidence-based conventional therapies. Alternative therapies, on the other hand, propose a unique model of disease that attempts to explain the entire complexity of health and illness [18]. Examples related to musculoskeletal care include osteopathy with its "law of the artery" and chiropractic care with its "law of the nerve" [19]. These types of therapies often resist verification and falsity, where verification is understood as the biological plausibility of their hypotheses and falsity as admitting that if their effects are not superior to a placebo, they cannot be considered evidence-based techniques [20,21].

The classification of these CAMs indicates that none have been subjected to rigorously designed and executed scientific studies that address essential questions such as their biological plausibility or clinical effectiveness. In contrast, when these therapies respond favorably to the scientific method, they are removed from the lists of CAMs and integrated into the repertoire of evidence-based techniques [22]. The importance of this discussion lies in the fact that in the best-case scenario, CAMs may not have a direct adverse effect. However, for many patients, they can be counterproductive by significantly delaying appropriate treatment and preventing or interfering with access to quality healthcare based on the scientific method [23].

In this context, there is a growing need for a critical comprehensive review of CAMs used in musculoskeletal care, focusing on their biological plausibility, clinical effectiveness, and the factors involved in clinical responses and effects, including potential mechanisms of action, contextual factors, placebo response, and psychological influences such as cognitive biases (Figure 1).

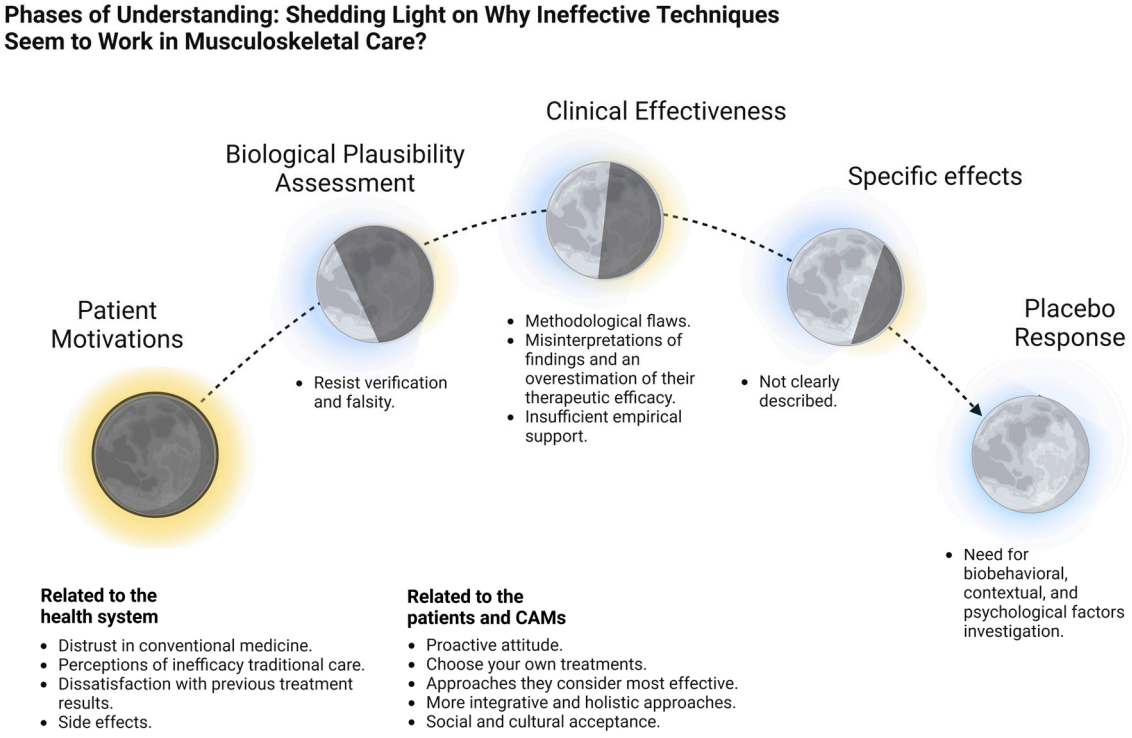

Figure 1. Phases of understanding: shedding light on why ineffective techniques seem to work in musculoskeletal care. This graphical abstract illustrates the progressive phases explaining why some ineffective techniques seem effective in musculoskeletal care. Represented by lunar phases, the graphic symbolizes the transition from the darkness of our current knowledge to the light this review aims to shed. Each phase progressively illuminates key elements involved in the use of CAMs—osteopathy and chiropractic—in musculoskeletal care, bringing clarity to what was previously obscure. Created in BioRender. F, M. (2025) https://BioRender.com/g83d974, accessed on 26 January 2025.

This review aims to examine these key dimensions while maintaining a balanced perspective, offering practical implications for both clinical practice and future research. Specifically, it is intended to provide guidance on the appropriate integration of CAMs as a first line for musculoskeletal care. Furthermore, the review highlights the necessity for

robust, high-quality studies to address existing gaps in evidence, fostering open and constructive dialogue among healthcare professionals. This balanced approach is intended to support evidence-based decision-making, promote ethical clinical practices, and encourage the advancement of integrative healthcare research.

2. Methodology of Literature Search

This critical comprehensive review was conducted following a different search strategy to identify relevant literature on CAMs used in musculoskeletal care [24]. The search was performed in multiple databases, including PubMed, Scopus, Web of Science, and Cochrane Library. The search was limited to articles published in English, spanning from January 2000 to January 2025. A manual search of reference lists from included articles was also conducted to ensure that no significant studies were omitted.

Eligibility Criteria

Study selection for this narrative review followed predefined inclusion and exclusion criteria to ensure methodological rigor and alignment with the research objectives.

Eligible studies were those investigating the biological plausibility, underlying mechanisms of action, or clinical efficacy of CAMs, specifically osteopathy and chiropractic, in musculoskeletal care. The study types included narrative reviews, systematic reviews, meta-analyses, original research articles, theoretical papers, and opinion/commentary articles. This broad scope allowed for the generation of hypotheses regarding the mechanisms underlying the use of CAM in musculoskeletal health. The comprehensive approach adopted in this review facilitated the inclusion of diverse sources, enriching the understanding of CAMs role in musculoskeletal care.

Studies were excluded if they focused on non-musculoskeletal conditions or primarily addressed psychological or wellness outcomes that were not directly relevant to musculoskeletal care. However, studies examining psychological effects (e.g., biases, anxiety, depression) as part of a broader analysis of CAM interventions in musculoskeletal conditions were included when they provided meaningful insights into the overall impact on patient well-being.

3. Biological Plausibility of CAMs

The discussion surrounding the biological plausibility of osteopathy and chiropractic in musculoskeletal care is a crucial aspect that demands careful analysis. Understanding the challenges inherent in the theoretical models underpinning these therapies is essential for evaluating their validity.

According to Koterov [25], biological plausibility serves as a fundamental pillar for establishing causal relationships in epidemiological research and health sciences. The concept rests on the premise that a causal link should conform to the prevailing scientific theories and align with the body of biological knowledge available. For an association to be deemed causal, it is essential to identify a coherent biological pathway that clarifies how one factor might influence another. In the absence of such a model, it is difficult to definitively confirm causality. This becomes especially critical in public health, where decisions regarding prevention and safety standards hinge on the validity of the scientific basis supporting the therapies being recommended or implemented [25].

3.1. Biological Plausibility of Osteopathy

Osteopathy was founded by the American physician Andrew T. Still, and claims that "somatic dysfunctions" in the musculoskeletal system are linked to both musculoskeletal and non-musculoskeletal conditions, considering osteopathic manipulative treatment as

the main intervention to treat these dysfunctions. Somatic dysfunctions can affect the skeletal, vascular, and neural systems and can originate pain, organ dysfunction, or impaired systemic health, highlighting the interconnection between the musculoskeletal system and other body systems [26]. This approach suggests that osteopathic manipulative treatment can address a wide array of clinical conditions, from substance abuse to musculoskeletal pain. However, this broad application risks undermining the scientific credibility of osteopathic practice, potentially leading practitioners to disregard established scientific consensus and perpetuate epistemological gaps in their practice [27].

Osteopathy is based mainly on three large groups of treatments or interventions: structural osteopathy, craniosacral osteopathy, and visceral osteopathy.

Structural osteopathy places emphasis on the interconnectedness of body systems and the body's inherent self-healing capabilities. Dysfunctions within the musculoskeletal system may affect visceral organs via somatovisceral reflexes, while visceral pathologies may present as restricted movement or modification in the tissue consistency in the musculoskeletal system, termed viscerosomatic reflexes [26]. Osteopathic manipulative treatment aims to correct these dysfunctions by relieving pain and improving range of motion, as well as improving neurovascular and lymphatic flow [26,28]. However, the efficacy of this approach is highly dependent on the identification of "somatic dysfunctions", a process with limited inter-rater reliability between practitioners [29].

Craniosacral osteopathy is based on the premise that alterations in the mobility of cranial sutures can cause diseases, disorders, or dysfunctions. It is argued that a disruption in the "mobility" of the sphenobasilar synchondrosis could lead to disturbances throughout the cranial complex, a diagnosis typically made through specific palpatory assessment by an osteopath. This approach often employs general concepts of proven biological phenomena to infer that similar processes occur within the osteopathic model. For instance, rhythmic movements observed from the cellular level to the cardiac level are used to suggest that the craniosacral system and its surrounding structures must exhibit a similar oscillatory rhythm [30]. However, it is noteworthy that findings from magnetic resonance imaging (MRI), which suggest that the skull might exhibit dimensional variations of 0.898 mm/pixel (less than a millimeter) [31], are often dismissed due to potential interpretation errors [30]. These results could stem from vestibular system stimulation, generating rhythmic head movements. Nevertheless, there is skepticism about the ability of manual therapists to perceive these submillimetric changes with their hands, as such variations fall outside the resolution capacity of MRI [31,32].

Finally visceral osteopathy proposes that manual manipulation can improve the mobility of internal organs and restore their function, based on the idea of interconnection between visceral and musculoskeletal structures [33]. However, studies investigating this supposed visceral mobility through osteopathic techniques have yielded inconsistent and inconclusive results. Moreover, the biomechanical and physiological principles supporting this notion lack grounding in human anatomy and physiology. While it is observed that viscera exhibit mobility during vital functions such as breathing and activities like running and jumping [34], a clear causal relationship between the alleged alteration of visceral mobility in various clinical conditions and the manual manipulations intended to restore it has not been established. Furthermore, osteopathy often falls into the fallacy of anatomical possibilism, exaggerating anatomical-functional relationships to the point of implausibility [35]. Additionally, the reliability of diagnostic techniques used in visceral osteopathy lacks solid evidence, and there is no consensus on the existence of "somatic dysfunction" [36,37].

3.2. Biological Plausibility of Chiropractic

Chiropractic was founded by David Palmer and is mainly based on the theory of "vertebral subluxation", which claims that misaligned vertebrae can cause interference in the nervous system, subsequently affecting the function of other bodily systems, such as the immune system, and contributing to the development of diseases [38,39]. However, this theory has sparked intense debate and controversy within the scientific community due to the lack of robust evidence supporting its biological plausibility [40,41]. Moreover, the treatment for this proposed complex and multisystemic dysfunction involves spinal manipulation or chiropractic adjustment, which many consider an effective tool for relieving ailments and improving neurological function [42]. Proponents of chiropractic argue that these are specific assessments and maneuvers aimed at correcting vertebral subluxations. Nevertheless, studies have shown that segmental vertebral evaluation and manipulations cannot be specifically applied to a particular vertebra and that their limited effects are based on nonspecific mechanisms [43].

In the discussion of new causal mechanisms, two general errors or biases can occur, identified as "the believers and the skeptics" [44]. The first error, the believer's error, is inferring the existence of a causal mechanism when it does not exist where osteopathy, chiropractic care, and other CAMs may fall. The second, the skeptic's error, is inferring the nonexistence of a causal mechanism that exists, an error we must strive to avoid until evidence suggests otherwise. In this sense, osteopathy and chiropractic describe a causal mechanism that is not supported by biological bases; therefore, its effects may rely on nonspecific, placebo, and contextual factors [45,46]. On the other hand, conventional interventions such as exercise have described multiple mechanisms of action with strong biological bases, specific effects and long-term effects.

The reviewed articles encompass a wide range of study types, including observational studies, reviews (narrative, systematic, and conceptual), and educational model validations. Interventions analyzed focus primarily on osteopathy, chiropractic care, visceral mobilization, and spinal manipulation. Populations studied ranges from the general public to patients with spinal pain, pediatric groups, and osteopathy students. Key outcomes include assessments of clinical efficacy, biological plausibility, and theoretical mechanisms. However, the studies are frequently limited by theoretical frameworks, small sample sizes, and a lack of robust experimental evidence. The reader can find the studies analyzed in Appendix A.

4. Clinical Effectiveness of Osteopathy and Chiropractic in Musculoskeletal Care

4.1. Clinical Effectiveness of Osteopathy

Osteopathy, encompassing structural, visceral and craniosacral techniques, has been subject of debate regarding its efficacy in musculoskeletal care. Although the effectiveness of pragmatic osteopathy has been studied in some systematic reviews with meta-analyses [47–51], and associated with small statistical effects on clinical outcomes, the methodological flaws identified cast doubt on the positive results. The most important biases found were the inclusion of congress abstracts, pilot studies that do not aim to evaluate clinical effectiveness, and unpublished materials from osteopathic institutions as relevant studies. Recent systematic reviews with meta-analyses with more robust methodological approaches found that pragmatic osteopathic manipulative treatments, and visceral and craniosacral osteopathy in isolation produced no statistically significant effects on clinical outcomes on patients with musculoskeletal or non-musculoskeletal disorders [36,52–58]. Specifically, a recent systematic review and meta-analysis demonstrated that the pragmatic application of osteopathic manipulative treatment was not superior to sham or

placebo interventions for patients with neck and low back pain. This finding suggests that the effects of osteopathy may be attributed more to placebo effects than to specific therapeutic mechanisms [29].

Several critical methodological issues and biases have been identified in primary clinical trials. One of the most significant concerns is the diagnosis based on the manual palpation of so-called somatic dysfunctions, whose reliability has been shown to be questionable due to poor inter-examiner agreement and the inability to standardize this method. Additionally, there is a lack of standardization in the parameters of the techniques employed, such as the applied force, the duration of the interventions, and the pragmatic application based on palpatory findings.

Other relevant factors include the use of placebo techniques with questionable efficacy, the absence of proper evaluation of masking effectiveness, the use of small sample sizes, and the presence of groups with high variability and elevated standard deviations. These methodological shortcomings significantly undermine the robustness and validity of the results obtained [56,59–62].

4.2. Clinical Effectiveness of Chiropractic

Chiropractic care faces similar scrutiny regarding its clinical effectiveness. It is often criticized for lacking a plausible biological model for its interventions. While short-term improvements in spinal symptoms are modest, these often lack clinical significance [63,64]. Moreover, chiropractic interventions have not demonstrated superiority over other treatments, and their effectiveness compared to placebo or no intervention remains questionable [65,66]. The use of chiropractic care for conditions unrelated to the spine is not supported by evidence [67].

Spinal manipulation is the cornerstone of chiropractic care and has been associated with frequent mild adverse effects and, in rare cases, severe complications of unknown incidence [68]. Chiropractors appear to have the highest number of adverse events following manipulations among healthcare professionals [69], while the low quality of evidence regarding sham manipulation introduces further uncertainty in comparisons between interventions.

The reader can find the studies analyzed in Appendix B.

5. Effects and Potential Mechanisms of Osteopathy and Chiropractic in Musculoskeletal Pain

The overall treatment effect is divided into three interacting factors: specific, contextual, and non-specific. Specific effects are clinical changes due to the direct mechanisms of the intervention. Contextual effects, on the other hand, result from the therapeutic encounter and the context of the health care system. Finally, non-specific effects, such as the natural course of the disease or regression to the mean, influence the clinical response but are not related to the intervention. The sum of contextual and non-specific effects is called the placebo response, based on changes perceived by the patient independently of the specific effects [45,46]. It is important to clarify that these factors influence each other and cannot be completely isolated (Figure 2).

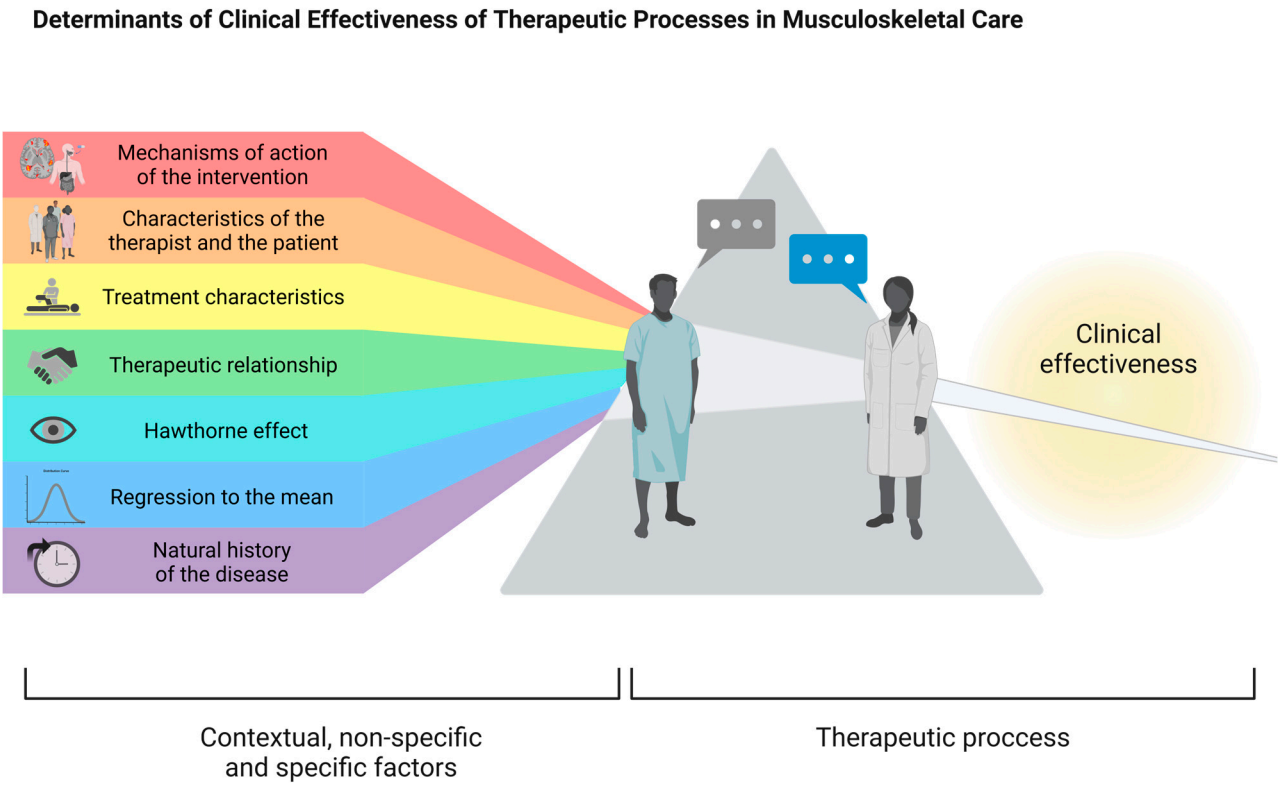

Figure 2. Determinants of the clinical effectiveness of therapeutic processes in musculoskeletal care. The clinical effectiveness of a therapy extends beyond the results of controlled studies, as it is influenced by a complex interaction between the specific effects of a therapeutic intervention and contextual and non-specific factors [45,46]. Non-specific effects include the natural history of the disease, fluctuations in symptom severity, regression to the mean, measurement errors, or the Hawthorne effect; while contextual factors include characteristics of the therapist and patient, the relationship between them, characteristics of the treatment, and the healthcare setting. These are just a few examples, but many more factors can be considered. Illustration adapted from Hohenschurz-Schmidt et al. [70]. Created in BioRender. F, M. (2025) https://BioRender.com/g83d974, accessed on 26 January 2025.

5.1. Specific Factors in Osteopathic and Chiropractic Practices for Musculoskeletal Care

Specific factors for osteopathy and chiropractic have not been clearly demonstrated yet. Spinal manipulation therapy (SMT) is probably the most investigated technique that has shown some biological plausibility and is a common technique used by both osteopaths and chiropractors.

SMT is proposed to alleviate musculoskeletal pain through various neurophysiological mechanisms. At the peripheral level, the spinal manipulation may reduce proinflammatory cytokine activity and oxidative stress, potentially mitigating inflammation and peripheral sensitization [66]. At the spinal level, SMT is believed to induce segmental inhibition, which decreases temporal summation of nociceptive signals, thereby dampening central sensitization processes [71,72]. These effects have been observed in increased pain pressure thresholds in corresponding dermatomes and myotomes, as well as reduced sensitivity to thermal stimuli [73].

However, while SMT influences these neurophysiological parameters, these changes often fail to correlate consistently with improvements in pain, stiffness, or functional outcomes [74]. Furthermore, descending inhibitory pathways may contribute to reduced pain

perception, but it remains unclear whether this is a specific result of SMT or attributable to non-specific or contextual factors [75]. It has been proposed that efforts are needed to improve the quality of studies and methods in order to know whether there are specific effects of these interventions and what their real contribution is to the overall effect of clinical outcomes [76].

5.2. Placebo Response: Interaction Between Non-Specific and Contextual Factors in Osteopathic and Chiropractic Practices for Musculoskeletal Care

The placebo and nocebo effects are therapeutic responses that arise independently of the intrinsic efficacy of an intervention. Specifically, the nervous system determines whether a treatment response is perceived as favorable or not [77–79]. These phenomena, which can be either positive or negative, are rooted in behavioral, emotional, and cognitive modulation [78,79].

The placebo response encompasses a wide range of factors, including personality traits [80,81], the patient–therapist relationship [82,83], cultural influences [84,85], genetics [78], conditioned responses [86], observational learning [87], descending modulation mechanisms [88], and brain dynamics [79,89]. These factors seem to contribute significantly to the outcomes observed in CAMs [90]

The placebo response is inseparable from clinical practice and is triggered by the sum of the interaction of contextual and non-specific factors. However, it is important to note that relying on therapies that depend solely on the manipulation of these factors leads to clinical responses with great variability and unpredictability [91,92]. Furthermore, the long-term stability of these effects is uncertain, suggesting that they may be of limited value and may interfere with appropriate treatments [93]. CAMs may also generate a nocebo response, which could worsen the patient's condition.

Contextual and psychological factors are fundamental to the placebo phenomenon [84,94]. Therapies such as osteopathy or chiropractic often leverage these elements, intentionally or not [95]. For instance, in conservative, primarily passive treatments for patients with non-specific chronic low back pain, about half of the overall treatment effect can be attributed to non-specific effects that occur without any treatment rather than to specific effects or placebo effects induced by the therapies [96].

It is important to recognize that the placebo response represents only one facet of the numerous variables influencing the interaction between a patient, therapist, and clinical situation. The outcomes of any given intervention can be affected by non-specific effects, such as the natural history of the disease, regression to the mean [46], or the expectations generated by the therapy [97].

5.3. Cognitive-Mediated Effects and Bias in Osteopathic and Chiropractic Practices for Musculoskeletal Care

Emotional, cognitive, and social factors play a pivotal role in how individuals respond to therapy. The attention, care, emotional support, and explanations provided during treatment can significantly influence the patient's experience, irrespective of the treatment's actual efficacy [90].

The meaning attributed to a symptom and the approach taken towards it are crucial in determining the therapeutic response. For example, postoperative pain, which may be perceived as part of the healing process, can be experienced and tolerated differently compared to pain associated with a terminal illness, which is often linked to death and a palliative approach [98]. Some CAMs offer alternative narratives that allow patients to reinterpret their experiences, thereby enhancing their psychological well-being. Participation in therapy groups or communities that support these practices can provide a sense of belonging and social support, which contributes to emotional well-being [99–101].

These psychological responses are further influenced by cognitive biases defined as systematic patterns that can distort perception, memory, and reasoning and lead to erroneous conclusions or suboptimal decisions [102]. Such biases can arise from altered information processing [103], past experiences [104], personal beliefs and learning about health, illness, and care processes [102,105] as well as social and cultural influences [102].

The literature highlights several cognitive biases, such as causality bias and authority bias, that appear to play an important role in the therapeutic context. Furthermore, biases such as optimism bias, illusion of control bias, and confirmation bias may also influence the dynamic between patient and therapist, potentially shaping treatment perceptions and outcomes.

Causality bias occurs when a specific outcome is mistakenly attributed to a particular action, often due to a low demand for evidence [103,105]. Individuals prone to this bias tend to attribute any change in their health to a practice that aligns with their beliefs or previous experiences [106].

Authority bias occurs when the opinion of an expert, such as a health professional, is deemed sufficient for decision-making by the patient [107]. Research has shown that many health practices not supported by scientific evidence are recommended by professionals, who may themselves have limited understanding of the practice they endorse [108–110].

Optimism bias reflects the tendency to overestimate positive outcomes and underestimate potential risks [111], which can lead patients to believe that these therapies are inherently safe or more effective than the evidence suggests.

Illusion of control bias refers to the belief that one can influence outcomes beyond actual control; this can reinforce both patient and practitioner confidence in these interventions, even when objective evidence is lacking [111,112].

Confirmation bias further compounds these effects by particularly driving professionals to selectively interpret information that aligns with their pre-existing beliefs and dismiss contradictory evidence, thereby negatively interfering with clinical reasoning [109,113,114]. These cognitive distortions not only bias clinical decision-making but also highlight the importance of fostering critical thinking and promoting evidence-based practices to mitigate the impact of these biases in musculoskeletal care.

Additional psychological effects relevant to the interpretation of CAMs include the Barnum effect and the Hawthorne effect. The Barnum effect, often exploited in pseudoscientific fields, occurs when individuals perceive vague and generic descriptions as highly accurate and personalized [115]. In practices like osteopathy and chiropractic, this effect leverages patients' desires for diagnostic certainty and the need to identify predictable patterns in their health, fostering a sense of personal connection with the treatment and practitioner [116–118]. This perceived personalization can bypass critical reasoning, leading patients to trust vague explanations and interpret ambiguity as hidden meaning, which reinforces their belief in the therapy's effectiveness despite a lack of scientific evidence [119]. As a result, emotional shortcuts in decision-making may drive continued adherence to such treatments, amplifying their perceived benefits [120].

The Hawthorne effect suggests that patients may modify their behavior and report therapeutic improvements simply due to their participation in treatment that includes regular and personalized follow-up by the therapist. This phenomenon is particularly evident in therapies where the evaluation criteria are subjective, such as pain or "dysfunction" [121]. Patients might exaggerate symptom improvements to align with the therapist's expectations, leading to an overestimation of treatment efficacy in both effective and ineffective approaches [122,123]. Additionally, the exposure to a therapeutic ritual with promised results can shape symptom perception and evaluation, with many patients confirming expected changes to satisfy the therapist [123].

While these psychological factors are common to varying degrees among all individuals, certain traits appear to increase susceptibility to persuasion by these types of therapies and narratives. Characteristics such as agreeableness, introversion, and lack of premeditation are associated with greater susceptibility [124,125].

The studies used in this section employ diverse methodologies, including experimental research, surveys, qualitative studies, systematic reviews, and meta-analyses. They examine psychological elements such as placebo effects, cognitive biases, pseudoscientific beliefs, causal illusions, and the "Guru Effect", with populations including CAMs users, patients with cancer or rheumatoid arthritis, university students, and physicians. Outcomes emphasize the cognitive, social, and cultural influences on beliefs in CAMs, highlighting mechanisms like prior expectations, causal illusions, and health-related judgments. However, limitations include small sample sizes, reliance on self-reports, and theoretical models alongside limited generalizability and potential biases such as recall or selection. The reader can find the studies analyzed in Appendix C.

5.4. The Effects Mediated by Context in Osteopathic and Chiropractic Practices for Musculoskeletal Care

Contextual factors in the therapeutic interaction between patients and healthcare providers encompass a wide range of elements. These factors extend beyond the specific actions of the treatment and include the physical environment, the quality of the relationship with the professional, the patient's expectations, and the perceived credibility of the therapist. Additionally, rituals, healing cues, and other symbolic elements associated with the treatment process may also play a significant role in the patient's response [126].

Often, expectations and perceptions of outcomes differ between the healthcare provider and the patient, which can lead to dissatisfaction with conventional care. This dissatisfaction is a key factor driving patients toward CAMs [127]. A patient's expectations regarding the effectiveness of a therapy can significantly influence their perception of treatment outcomes [9,125]. If a person anticipates improvement, they are more likely to perceive a benefit, even if the treatment is objectively ineffective. Conversely, negative expectations can lead to unfavorable perceptions of outcomes, regardless of the treatment's objective efficacy. Previous positive experiences can also enhance the response to treatment; for example, individuals who have had success with osteopathic or chiropractic manipulations are more likely to respond favorably to similar treatments in the future [128].

This influence of expectations has been observed by Bialosky [129] inducing positive and negative expectations in a group of patients with low back pain. Subjects who were given positive expectations about the effects of lumbar manipulation experienced a reduction in pain (hypoalgesia) in the treated area. Conversely, those who received negative expectation instructions reported an increase in pain perception (hyperalgesia) in the same region. Interestingly, these changes in pain perception were localized to the region where manipulation was expected to have an effect, with no significant impact on the lower extremities where no expectations were set.

Rituals and ceremonies associated with CAMs can also influence the patient's perception of treatment effectiveness, contributing to perceived therapeutic effects [116,130]. The "efficacy paradox" illustrates how a complex intervention, such as visceral manipulation or craniosacral mobilization, may have minimal specific effects but a large placebo effect. In contrast, conventional treatment with moderate specific effects but a smaller placebo effect may be perceived as less effective by the patient [130]. The complexity of an intervention often correlates with its perceived effectiveness (Figure 3).

This efficacy paradox has been studied in recent studies. Some patients report significant pain relief after osteopathy and chiropractic sessions primarily based on

manipulation. These positive outcomes are short-term and largely attributed to placebo response, mainly driven by personalized care, the therapist–patient relationship, the time dedicated by the practitioner, and the perception of specificity for a particular issue. However, current evidence indicates no significant differences in their application methods, and their use should be prioritized based on patient comfort and preferences [131]. In contrast, therapeutic exercise has strong evidence supporting its effectiveness in improving pain and function in the long term. However, its effects may take longer to manifest and require active patient commitment, which can reduce adherence and the perceived outcomes.

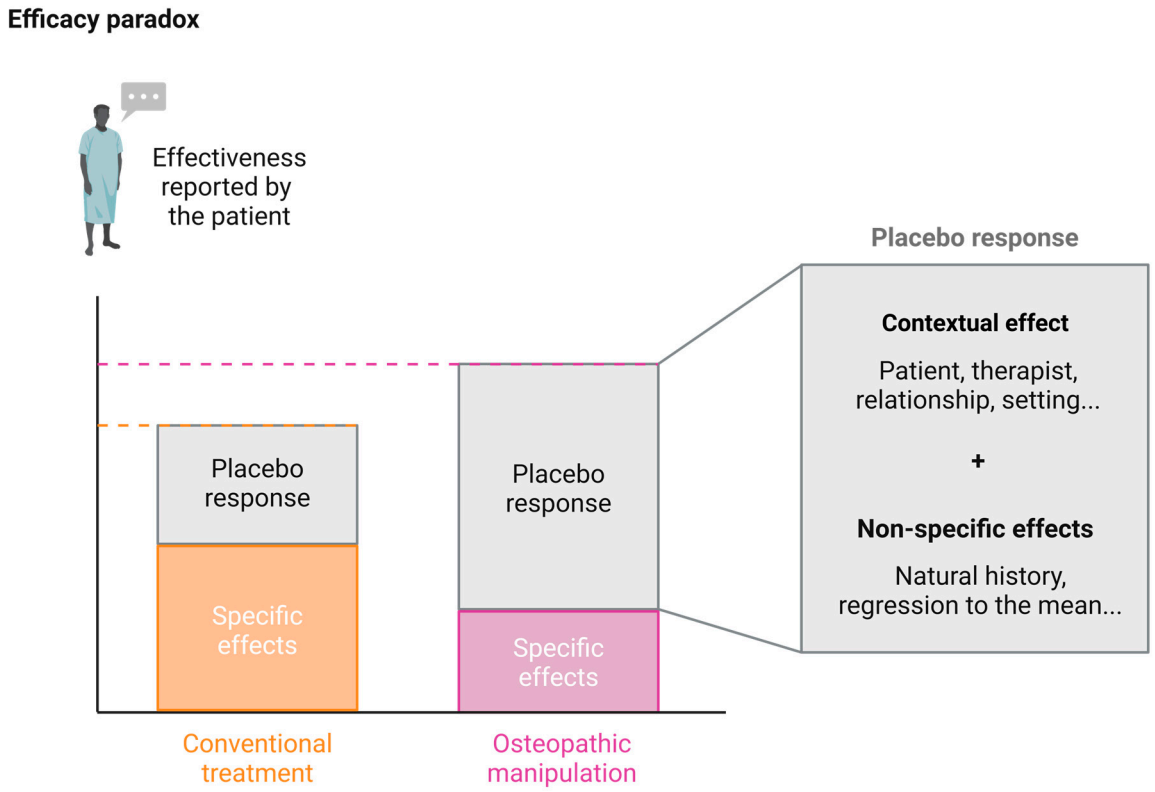

Figure 3. Efficacy paradox: The efficacy paradox focuses on the discrepancies between the results perceived by the patient and the real effectiveness of the intervention. In the case of osteopathy and chiropractic, it focuses on the interaction between the demonstrated specific effect of the technique and the significant influence of the placebo responses, mediated by the effects of non-specific factors and the therapeutic context, such as the complexity of the therapeutic ritual or the expectations generated by the therapist [46,132] Created in BioRender. F, M. (2025) https://BioRender.com/g83d974, accessed on 26 January 2025.

Thus, the positive outcomes perceived by some individuals during the application of certain low-value techniques appear to be more related to the inherent characteristics of the therapeutic process than to the physical intervention itself. These characteristics may include the environment in which the therapy is conducted, the theoretical framework underlying the approach, the evaluation performed in each session, therapeutic touch, and the patient's active involvement in their treatment [133–135]. Therefore, it is crucial to assess the contextual effects that may influence the individual, their condition, the intervention, and the outcome to determine the relevance of a particular intervention in each specific clinical setting [136]. These factors are often present in practices such as osteopathy and chiropractic, and they can lead to confusion on the part of the therapist regarding

the actual effects of the applied techniques [95]. While the perceived benefits may be substantial, it is important for practitioners to distinguish between the therapeutic value of contextual factors and the specific efficacy of the techniques themselves.

5.5. Neurobiological Basis of Contextual Effects in Osteopathic and Chiropractic Practices for Musculoskeletal Care

The effects mediated by the context, such as placebo and nocebo effects, are modulated by various neurobiological systems, including opioid, endocannabinoid, and dopaminergic systems, which play an essential role in the modulation of pain and reward pathways [79,137,138]. These systems contribute to the analgesic effects observed in response to treatments, even in the absence of a specific intervention. Furthermore, placebos can influence serotonergic pathways, affecting emotional regulation and mood [137,139]. Placebo effects are also mediated by the interaction between cholecystokinin (CCK) and endogenous opioids, which regulate both positive and negative effects [138,140].

The neural modulation arising from these contextual effects involves a functional connection between several brain regions, such as the dorsolateral prefrontal cortex (CPFDL), the rostral anterior cingulate cortex (rACC), and subcortical regions such as the hypothalamus (HYP), amygdala (AMYG), and periaqueductal gray (PAG), which play a crucial role in placebo-induced analgesia [79,141,142]. During placebo analgesia, decreased neural activity is also observed in pain-associated regions, such as the thalamus and primary somatosensory cortex, and could potentially contribute to a subjective reduction in pain perception [78]. Furthermore, placebo effects also modulate spinal cord activity and descending analgesia pathways, reinforcing the influence of contextual factors on pain relief [143,144]. There are studies suggesting that brain morphology and functional connectivity can predict individual responses to placebo-induced analgesia [145,146]. Conversely, abnormal activation of the hippocampus (Hp) has been linked to nocebo effects, as this region, along with the AMYG, is involved in processing emotions such as anxiety and distress [79].

Differing instructions and expectations regarding the same procedure can alter the nervous system's response. It has been observed that when people are informed about the therapeutic efficacy of a technique, there is an increase in activity in regions such as the ventral striatum, associated with the reward circuit, and a decrease in activity in secondary somatosensory regions and the right dorsolateral prefrontal cortex. However, this change in activity does not occur when people are told that the technique may be painful or ineffective [147] (Figure 4). These findings suggest that the therapeutic context may have a more significant impact than the intervention itself.

While this evidence marks significant progress in understanding these therapeutic phenomena, research findings remain heterogeneous, and further exploration is needed to better understand the neurobiological mechanisms of these effects [148].

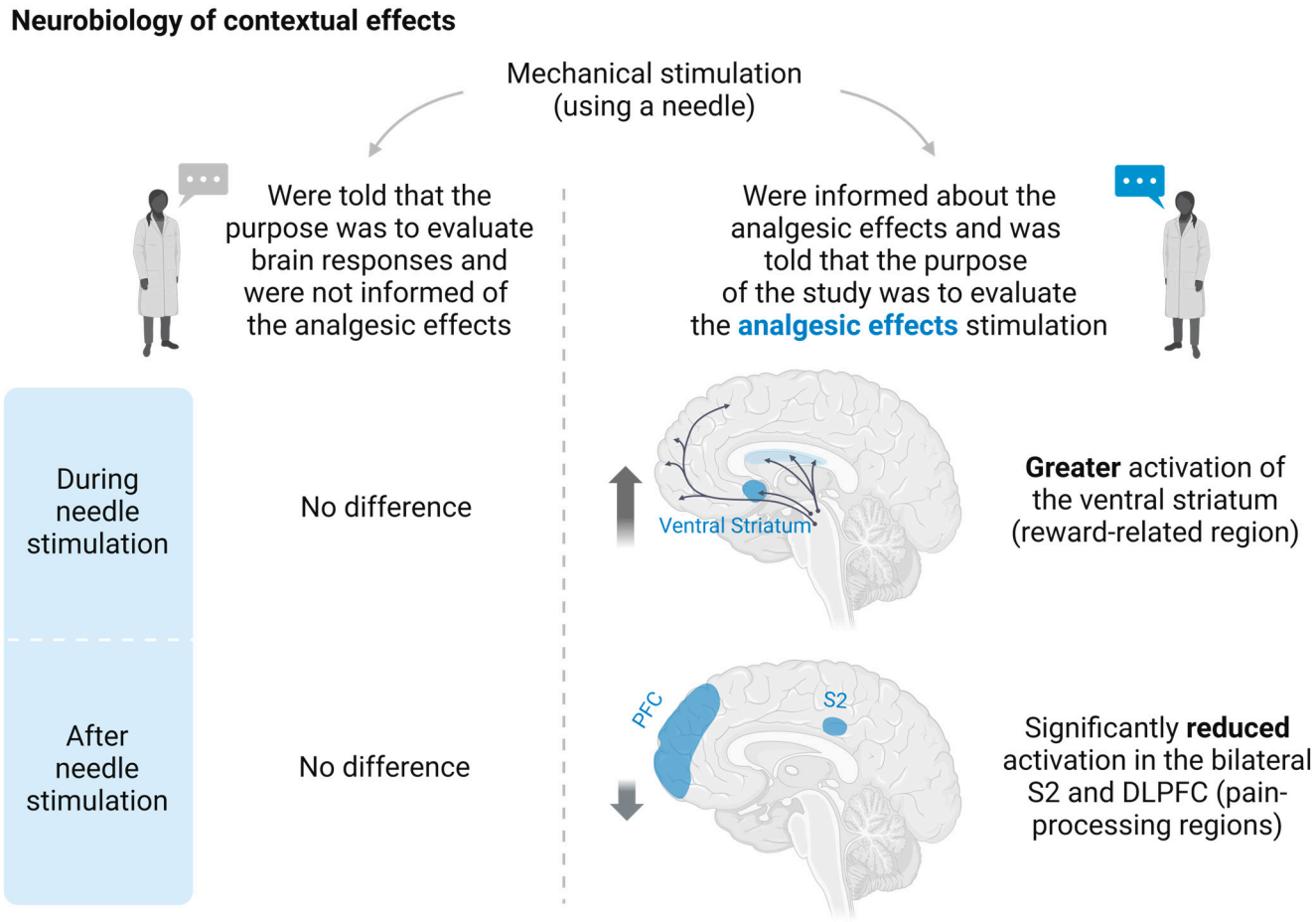

Figure 4. Neurobiology of Contextual Effects: The instructions given to patients and the expectations created about a health intervention seem to trigger neurobiological changes that align with the patient's perception of the treatment's effectiveness. This phenomenon highlights the significant role of cognitive and contextual factors in shaping therapeutic outcomes. Studies suggest that patient expectations can influence both neurophysiological responses and perceived benefits [147]. Created in BioRender. F, M. (2025) https://BioRender.com/g83d974, accessed on 26 January 2025.

For the analysis of Section 5, the following articles were analyzed, spanning various study types, including narrative reviews, randomized controlled trials, systematic reviews, pilot studies, and meta-epidemiological analyses. They examine placebo and contextual effects in CAMs, with a focus on interventions like osteopathy, chiropractic and treatments for chronic pain and migraines. Populations include patients with chronic and musculoskeletal pain as well as general recipients of CAMs. Key outcomes highlight the role of placebo, nocebo, and contextual factors in shaping treatment perceptions and outcomes, particularly discrepancies in patient expectations. Common limitations include reliance on theoretical frameworks, small sample sizes, lack of control groups, and high heterogeneity in study designs, reducing applicability to specific populations. The reader can find the studies analyzed in Appendices C–E.

6. Ethical Considerations of the Effects Mediated by Context and Placebo as First-Line Musculoskeletal Therapy

The potential mechanisms underlying the effects of osteopathy and chiropractic in musculoskeletal care remain a matter of debate. On one hand, some studies suggest that specific biological mechanisms may play a role in these therapies, but these mechanisms

are poorly understood and require further research [28,76]. On the other hand, most recent evidence highlights the biological implausibility of these CAMs. Even practitioners in these fields exposed the challenges in designing convincing and contextually relevant control interventions, which can significantly influence placebo effects across study groups [132]. Consequently, research findings must be interpreted with caution due to various methodological factors that contribute to a high risk of bias.

Integrating biologically implausible therapies, whose potential mechanisms may rely primarily on placebo effects (contextual and non-specific factors) into healthcare systems raises significant ethical dilemmas. CAMs such as osteopathy and chiropractic may lead to: (1) direct harms (i.e., side effects from cervical manipulation at maximum range of motion [69] or indirect harms (i.e., delaying an effective treatment); (2) emotional or financial harms, particularly for individuals with lower socioeconomic status; (3) wasted clinical resources; and (4) inequities in healthcare delivery.

Although osteopathy and chiropractic have built a substantial body of evidence over the years, clinical trials have consistently failed to demonstrate specific effects for improving various clinical conditions according to the most recent systematic reviews and meta-analyses [29,57,67,149]. For this reason, these therapies are still considered CAMs and have not evolved to conventional medicine. Consequently, their use by health care professionals for musculoskeletal care cannot be recommended. Scientific disciplines must rigorously challenge their own hypotheses and evolve their practices based on evidence. This case should not be an exception.

7. Implication for Clinical Practice

In many countries, these interventions are mandated to be performed by healthcare professionals, inadvertently lending them credibility through association with established musculoskeletal care practices. While it is unlikely that such therapies will disappear, nor is it the intention of this publication to advocate for their elimination, they must be critically evaluated to ensure their safety and efficacy. These practices should not be endorsed or integrated into musculoskeletal care without sufficient scientific validation.

At their current stage of development, most recent reviews and meta-analyses have shown CAMs such as osteopathy and chiropractic to be no better than placebo interventions or natural disease progression. Consequently, their clinical effectiveness is often overestimated, and they cannot be recommended as first-line treatments. This underscores the urgent need for robust, high-quality research to validate their efficacy and mechanisms. Rather than perpetuating a divide between disciplines, fostering constructive dialogue and collaboration between professionals is crucial for advancing integrated healthcare practices. This balanced approach will help ensure that only therapies with demonstrated value for musculoskeletal care are incorporated into mainstream practice, ultimately improving patient outcomes and promoting evidence-based decision-making.

Limitations

This review, while comprehensive, has several limitations that merit acknowledgment. First, as a comprehensive review, the methodology allows for the inclusion of subjective interpretations during the synthesis of evidence. Despite efforts to minimize bias, the absence of a systematic review framework may reduce replicability and introduce selection bias into the literature analyzed.

Second, many of the studies reviewed exhibit significant methodological shortcomings. These include small sample sizes, inadequate control groups, and a reliance on observational designs rather than experimental approaches. Together, these factors weaken the robustness of the conclusions and hinder the generalization of findings to broader

clinical contexts. The substantial heterogeneity in study designs and varying levels of methodological quality further exacerbate these challenges.

Third, although the focus of this review is the use of CAMs in musculoskeletal care—particularly osteopathy and chiropractic—some conjectures are derived from studies investigating different techniques or clinical scenarios. These findings may not always be directly transferable to the specific domain of interest, thereby limiting their applicability.

Fourth, certain articles reviewed on biological and psychological mechanisms are not specifically oriented toward CAMs, reducing their relevance and generalizability to this field.

Five, it is likely that the changes observed by osteopaths and chiropractors in their patients◎symptoms are due to unconscious long-term effects, such as placebo responses and non-specific factors, rather than specific effects of the interventions. These effects have not been studied in the long term, and there is no known evidence on the medium- and long-term impacts of these therapies.

Finally, the limited and methodologically diverse body of literature addressing the biological plausibility and potential mechanisms of osteopathy and chiropractic in musculoskeletal care has created theoretical gaps. These gaps necessitated reliance on broader or indirectly related studies to propose hypotheses, which may introduce additional uncertainty.

These limitations highlight the urgent need for future research employing rigorous and standardized methodologies. Well-designed randomized controlled trials, larger and more representative sample sizes, and consistent reporting standards are essential to address the gaps identified in the existing literature. Such efforts will contribute to a clearer understanding of CAMs◎role in musculoskeletal care and ensure that clinical practice remains grounded in scientifically validated principles.

8. Conclusions and Future Perspectives

The growth of musculoskeletal care as a clinical field reveals a dark side, or perhaps a gray area, characterized by the increasing adoption of therapies lacking robust scientific evidence, which undermines the legitimacy of the discipline. Scientific knowledge is essential for advancing healthcare; however, it is inherently limited. The absence of evidence does not equate to falsity, and what is accepted as valid today may be refuted tomorrow. Thus, it is crucial to distinguish between the veracity of a claim and the quality of the available evidence. Nevertheless, reliance on methodologies that lack scientific rigor, even when they occasionally yield promising results, is neither prudent nor ethical.

In many countries, osteopathy and chiropractic care are delivered by healthcare professionals, a fact that—combined with their association with validated musculoskeletal care practices—inadvertently lends these therapies credibility through authority bias. However, these interventions often rely on theoretical models and mechanisms of action rooted in questionable biological plausibility. Diagnoses such as “somatic dysfunctions” or “vertebral subluxations” are inconsistent with established scientific knowledge. Conducting research based on these concepts poses significant challenges to validating the treatments proposed by these therapies, especially when they are founded on implausible anatomical and physiological beliefs.

Studies evaluating the clinical effects of these interventions are frequently marred by significant biases, including small sample sizes, the absence of standardized control groups, the use of inadequate assessment tools, and a reliance on observational designs. Furthermore, the lack of proper planning for controls or placebos can lead to erroneous interpretations by introducing contextual and non-specific factors that alter the dynamics between participants and therapists during research.

Key contextual and non-specific factors influencing outcomes include participants' expectations, amplified therapeutic rituals in the research setting, prior experiences with similar interventions, interactions with the research team, and variables such as the number, type, and timing of manual interventions. Additional influences include placebo effects, regression to the mean, and the natural history of the condition. These limitations hinder the generalizability of findings and reduce confidence in conclusions regarding the clinical effectiveness of these interventions.

Based on the current body of evidence, neither osteopathy nor chiropractic care can be recommended as first-line treatments for musculoskeletal conditions. Nonetheless, these practices are likely to remain part of clinical care due to cultural, historical, political, and patient preference factors. Therefore, it is imperative that these therapies undergo critical evaluation and are integrated into healthcare only when their safety and clinical efficacy are supported by rigorous scientific validation. By doing so, healthcare professionals can uphold their legitimacy, improve therapeutic outcomes, and foster informed decision-making.

Future research should prioritize addressing the limitations of the existing evidence base. This involves designing well-structured randomized controlled trials with larger, representative sample sizes and adequately planned control groups. Additionally, studies should incorporate approaches that consider contextual and non-specific factors, which, despite being often overlooked, appear to significantly impact clinical outcomes. Understanding these factors will contribute to a more accurate interpretation of the specific effects of osteopathic and chiropractic interventions. Furthermore, exploring advanced technologies—such as neurophysiological data analysis and its correlation with clinical outcomes—can provide greater precision in understanding the mechanisms of action of these therapies. Longitudinal studies are also essential to assess the long-term effects of these interventions, especially when integrated with evaluations of contextual and non-specific influences, which have been underexplored to date.

Finally, implementing evidence-based practices should be a priority, requiring healthcare professionals to actively stay informed and critically assess the methodological quality of published studies. To this end, we advocate for fostering a spirit of transdisciplinary and interdisciplinary collaboration among healthcare professionals and researchers to enhance methodological approaches and generate new evidence that optimizes clinical practice. Through this collective effort, the field of musculoskeletal healthcare can advance, promoting patient safety and delivering more effective treatments grounded in the best available scientific evidence.

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Appendix A. Biological Plausibility of CAMs

Author (Year)	Study Type	CAMs	Population	Outcomes and Limitations
Crow WT et al. (2009) [31]	Observational study	Osteopathy	Human calvarial structures	Outcomes: Statistically significant changes in cranial area. Changes above the resolution threshold of the MRI scanner (0.898 mm/pixel). Limitations: Limited resolution of the MRI scanner used. Small sample size (20 participants).
Mirtz et al. (2009) [42]	Epidemiological Review	Chiropractic	General chiropractic	Outcomes: Evaluated chiropractic subluxation using Hill's causation criteria, concluding it lacks validity as a disease cause. Limitations: Based on theoretical application without experimental data; potentially subjective interpretations.
Homola (2013) [40]	Commentary/Review	Chiropractic	General chiropractic	Outcomes: Critiqued the concept of "vertebral manipulation" in chiropractic, pointing out lack of scientific evidence for "vertebral subluxation". Limitations: No original research data provided. Findings are interpretive and based on existing literature, introducing potential bias.
Homola (2016) [41]	Narrative review	Pediatric chiropractic	Pediatric population	Outcomes: Criticized "vertebral subluxation" concept in pediatric chiropractic care, emphasizing lack of scientific support. Discussed potential health risks for children and need for appropriate medical referral. Limitations: No original research data provided. Findings are interpretive and based on existing literature, introducing potential bias.
Horton (2015) [33]	Clinical review			Outcomes:

				Identified potential clinical applications of VMT in treating genitourinary dysfunction. Outlined some clinical evidence supporting VMT for genitourinary and pelvic dysfunction. Limitations: Evidence limited primarily to case reports and observational studies. Lacks robust clinical and experimental trials. Effectiveness for specific conditions remains speculative. Proposed biological mechanisms lack empirical support.
		Visceral Mobilization therapy (VMT)	General population, focused on pelvic dysfunctions	
Côté P et al. (2020) [38]	Commentary/Review	Chiropractic	General population	Outcomes: Data linking chiropractic manipulation to immune system are unreliable. Lack of biological plausibility in relationship between chiropractic manipulation and immune system. Limitations: Does not provide new experimental data on biological mechanisms, relying on previous reviews and expert opinions.
Nim et al. (2021) [43]	Systematic review	Spinal manipulation	Patients with spinal pain	Outcomes: No significant difference between targeted and non-targeted manipulation sites, suggesting specificity may not impact treatment effectiveness. Limitations: Limited by small number of studies (10) and high variability in study designs. Differences in patient populations and protocols impact consistency of findings.
Requena-García J et al. (2021) [32]	Educational validation Model	Cranial osteopathy	Students learning cranial osteopathy	Outcomes: Relationship found between therapist experience and reliability in palpating cranial movements. Limitations: Use of cadaveric model limits transferability to real clinical situations. Variations in cranial movement, measured in microns,

				probably not perceptible by therapists.
Consorti G et al. (2023) [37]	Conceptual/Theoretical study	Somatic dysfunction	General population	Outcomes: Presents an enactive theoretical framework on "osteopathic dysfunction". Limitations: Lacks evidence on proposed potential neurobiological mechanisms. Does not establish clear relationship between proposed mechanisms and clinical situation.
Bordoni B, Escher AR. (2023) [30]	Review	Cranial osteopathy	General population	Outcomes: Inconsistencies in PRM theory highlighted. Cerebrospinal fluid (CSF) movement is inhomogeneous both centrally and peripherally. Limitations: No evidence that CSF movement is detectable by palpation. Strong suspicion that spheno-occipital synchondrosis is incapable of moving sacrum.
Hidalgo D et al. (2024) [35]	Narrative review	Osteopathy	Not applicable	Outcomes: Examines concept of "anatomical possibilism" in osteopathy. Argues this approach may lead to unsupported diagnostic and treatment practices. Emphasizes need for osteopathic interventions based on rigorous scientific evidence. Limitations: Lacks empirical data and relies on theoretical critique, which may introduce interpretative bias.

Appendix B. Clinical Effectiveness of Osteopathy and Chiropractic in Musculoskeletal Care

Author (Year)	Study Type	Musculoskeletal Care Practice	Population	Outcomes and Limitations
Ernst (2008) [68]	Evaluation of chiropractic practices, focusing on spinal manipulation and subluxation concepts	Chiropractic care	General population	Outcomes: Chiropractic care, particularly spinal manipulation, has been associated with frequent mild adverse effects and rare severe complications.

				Subluxation and spinal manipulation lack scientific backing. Spinal manipulation has only shown effectiveness for back pain. Many chiropractors treat non-musculoskeletal conditions without proven efficacy. The therapeutic value of chiropractic remains unproven beyond reasonable doubt. Limitations: Lack of empirical evidence for effectiveness beyond back pain. Incidence of severe complications from spinal manipulation is unknown. The review relies on existing literature, lacking new empirical data. No evidence for cost-effectiveness of chiropractic care.
Gross et al. (2010) [63]	Systematic review	Cervical manipulation and mobilization for neck pain	Adults with neck pain	Outcomes: Moderate quality evidence showed that cervical manipulation and mobilization produced similar effects on pain, function, and patient satisfaction at intermediate-term follow-up. Low quality evidence suggested cervical manipulation provided greater short-term pain relief than control. Low quality evidence also supported thoracic manipulation for pain reduction and improved function in acute pain and chronic neck pain. Optimal technique and dose need to be determined. Limitations: Low quality evidence for some outcomes. Methodological quality of studies varied (33% had low risk of bias). Limited evidence on the optimal technique and dose for manipulation and mobilization.
	Systematic review			Outcomes:

				Chiropractic interventions improved short- and medium-term pain and disability in acute and subacute LBP compared to other therapies. No significant difference for long-term pain or disability. Small improvements in short-term disability with chiropractic interventions compared to other therapies. No difference for chronic LBP. Limitations: Studies with high risk of bias. Small improvements in outcomes, with no clinically meaningful difference compared to other treatments. Limited evidence for chronic LBP and mixed populations. Need for better quality trials.
Walker et al. (2010) [64]		Combined chiropractic interventions	Adults with chronic low back pain	
Rubinstein et al. (2011) [150]	Systematic review and meta-analysis	Spinal manipulative therapy (SMT) for chronic low back pain	Adults with chronic low back pain	Outcomes: High-quality evidence suggests SMT has a small, statistically significant but not clinically relevant effect on pain relief and functional status in the short term compared to other interventions. Varying evidence for the effectiveness of SMT when added to other interventions. Very low-quality evidence for SMT's efficacy compared to inert or sham SMT. Limitations: No evidence of serious complications, but limited data on recovery, return-to-work, quality of life, and costs of care. Inconsistent quality of evidence for various outcomes. Sparse data on long-term effects and overall cost-effectiveness. High heterogeneity and variability in the studies.
Ernst (2012) [67]	Review	Chiropractic spinal manipulation	Patients with musculoskeletal and	Outcomes: Cautiously positive evidence for chiropractic spinal

			non-musculoskeletal conditions.	manipulation in treating low back pain and neck pain. Negative results for non-spinal conditions such as asthma and dysmenorrhoea. Cochrane reviews generally considered reliable but show limited evidence for effectiveness in certain conditions. Limitations: Clinical and statistical heterogeneity across studies prevented meta-analysis. Limited evidence for non-spinal conditions. Heterogeneity in the included studies made it difficult to draw definitive conclusions.
Ernst (2012) [52]	Systematic review	Craniosacral therapy (CST)	Various disorders	Outcomes: The review found that CST showed no substantial evidence of effectiveness for any condition. While low-quality studies suggested potential positive effects, the high-quality trial did not demonstrate any significant benefits. Limitations: The review included six studies, most of which had a high risk of bias. The methodological quality was generally poor, with only one study of higher quality. The positive effects suggested by low-quality studies were not corroborated by higher-quality trials, leading to doubts about the validity of CST's clinical benefits.
Ajimsha et al. (2013) [59]	Randomized controlled trial	Myofascial release	Nursing professionals with chronic lower back pain	Outcomes: MFR showed greater improvement in pain and disability compared to the control group. MFR group had a 53.3% reduction in pain and 29.7% reduction in disability at week 8, with continued improvement at week 12. 73% of MFR group had ≥50% pain reduction. Limitations:

				Single-blind design could introduce bias. No placebo for control group, only sham MFR. Small sample size (80 participants). The study did not address long-term effects beyond 12 weeks. The control group received sham MFR, which may not fully mimic the standard care.
Franke et al. (2014) [47]	Systematic review and meta-analysis	Osteopathic manipulative treatment (OMT)	Adults with non-specific low back pain	Outcomes: Moderate-quality evidence showed OMT significantly improved pain and functional status in acute and chronic nonspecific LBP. Limitations: Low evidence quality limits generalizability. The small number of included trials limits robustness. Future research requires larger, high-quality randomized controlled trials (RCTs) with robust control groups.
Guillaud et al. (2016) [53]	Systematic review	Craniosacral therapy (CST)	Various disorders	Outcomes: Diagnostic procedures used in cranial osteopathy are unreliable in many cases. For efficacy, the review found that the studies had significant methodological flaws, with only three studies showing low risk of bias. These studies failed to rule out non-specific effects, and no strong evidence supported the efficacy of cranial osteopathy. Limitations: Diagnostic reliability, there was inconsistency in the results, indicating a lack of reliability in cranial osteopathy diagnostics. The methodological quality of the included studies was generally low. High risk of bias. Low quality of the studies. The heterogeneity in study designs and methodologies may

				limit the generalizability of the findings.
Arguisuelas et al. (2017) [60]	Randomized controlled trial	Myofascial release	Adults with nonspecific chronic low back pain	Outcomes: Significant improvements in pain (SF-MPQ) and sensory subscale, compared to sham MFR. Disability and fear-avoidance beliefs significantly decreased in the MFR group compared to the control. No differences in VAS scores between groups. Limitations: The clinical relevance of the improvements is uncertain due to the 95% CI overlapping the minimal clinically important differences. The study was limited to a small sample size (54 participants). Short duration of the intervention (4 sessions). Lack of long-term follow-up data.
Kranenburg HA et al. (2018) [69]	Systematic review	Cervical spine manipulation (CSM) and mobilization	Patients with neck pain and headache	Outcomes: Identified characteristics of patients, practitioners, treatment process, and adverse events (AE). Cervical arterial dissection (CAD) reported in 57% of cases, with women more at risk. Limitations: Poor description of patient characteristics and under-reporting of cases. Further research needed for uniform AE registration using standardized terminology.
Rubinstein SM et al. (2019) [65]	Systematic review and meta-analysis	Spinal manipulative therapy (SMT)	Patients with chronic low back pain	Outcomes: SMT produces similar effects to recommended therapies for short-term pain relief and moderate improvement in function. Compared to non-recommended therapies, SMT shows a small to moderate improvement in function but minimal pain relief.

				Evidence for sham SMT is of low quality, suggesting uncertain effects. Musculoskeletal adverse events were transient and mild to moderate in severity. Limitations: High heterogeneity between studies made it difficult to interpret some findings. Evidence for the effectiveness of sham SMT was of very low quality. Most studies did not systematically report adverse events. Some results were not clinically relevant despite statistical significance. comparisons, heterogeneity in comparison treatments.
Rehman et al. (2020) [48]	Systematic review and meta-analysis	Osteopathic manual therapy (OMT)	Patients with chronic pain	Outcomes: Some improvement in pain and functional outcomes findings limited by inconsistent methodologies. OMT demonstrated no significant impact compared to physiotherapy or gabapentin for any measured outcomes. Limitations: Small sample sizes. Variability in techniques and outcomes. Heterogeneity among comparator treatments and outcome measures reduces generalizability.
Farra et al. (2021) [49]	Systematic review and meta-analysis	Osteopathic interventions (OMT, MFR, CST, OVM)	Patients with chronic non-specific low back pain	Outcomes: Osteopathic interventions are more effective than control treatments in reducing pain and improving functional status. Myofascial release (MFR) showed the most effective results for pain reduction, with moderate-quality evidence. Osteopathic manipulative treatment (OMT) showed a low-quality effect in pain reduction. Craniosacral therapy (CST) and osteopathic visceral

				manipulation (OVM) showed limited evidence for efficacy. Limitations: None of the studies were judged at low risk of bias (RoB). Low to very-low-quality evidence for some treatments, particularly for OMT and CST. Limited diversity in osteopathic treatment types, which hinders generalization of findings. Further high-quality trials are needed to better compare different osteopathic techniques.
Nguyen et al. (2021) [61]	Randomized clinical trial	Osteopathic manipulative treatment (OMT)	Adults with nonspecific subacute or chronic low back pain (LBP)	Outcomes: The standard OMT group showed a mean reduction in LBP-specific activity limitations of −4.7 points (Quebec Back Pain Disability Index) at 3 months, significantly better than sham OMT group (−1.3 points). No significant difference in pain reduction at 3 and 12 months. Serious adverse events reported in both groups but not related to OMT. Limitations: The effect of OMT on LBP-specific activity limitations is small and its clinical relevance is questionable. No significant differences found for secondary outcomes such as pain and quality of life. The study lacks long-term efficacy data, and the sham OMT may not fully replicate standard OMT in terms of patient expectations.
Farra et al. (2022) [50]	Systematic review and meta-analysis	Osteopathic manipulative treatment (OMT)	Adults with non-specific neck pain	Outcomes: Osteopathic interventions showed statistically significant improvements in pain levels and functional status compared to no intervention or sham treatments. Limitations: Small sample sizes. Difficulty standardizing techniques.

				Evidence quality was rated as "very low."
Lotfi et al. (2023) [51]	Literature review	Osteopathic manipulative teatment (OMT)	Patients with irritable bowel syndrome (IBS)	Outcomes: The review suggested that OMT may reduce IBS symptoms such as abdominal pain, bloating, and irregular bowel movements. Improvements were attributed to potential modulation of visceral function and nervous system responses. Limitations: Evidence relied on a small number of studies with varying methodologies and quality. Lack of high-quality RCTs and limited generalizability. The findings were based on limited and mixed evidence.
Ceballos-Laita et al. (2023) [58]	Systematic review and meta-analysis	Visceral osteopathy	Adults with low back pain	Outcomes: Visceral osteopathy did not show significant improvements in pain intensity, disability or physical function. High heterogeneity found in the pain intensity outcome. Limitations: High risk of bias in the included studies. Lack of high-quality studies evaluating the effectiveness of visceral osteopathy for LBP. The small number of studies included (5 studies, 268 patients) and heterogeneity in outcomes limit the reliability of conclusions.
Buffone et al. (2023) [55]	Systematic review and meta-analysis	Osteopathic manipulative treatment (OMT)	Irritable bowel syndrome (IBS)	Outcomes: OMT showed statistically significant improvement in abdominal pain and constipation, with effect sizes. OMT was not superior to control for other IBS symptoms such as severity of IBS, Likert scale ratings, and diarrhea. The quality of evidence was deemed "low" for abdominal pain and constipation, and "very low" for diarrhea. The evidence did not support the superiority of OMT for all IBS symptoms,

				OMT was found to be safe with no major adverse effects. Limitations: The methodological quality of the included studies was generally low. High risk of bias. Low quality of the studies. The heterogeneity in study designs and methodologies may limit the generalizability of the findings.
Silva et al. (2023) [54]	Systematic review	Visceral fascial therapy	Patients with visceral dysfunctions	Outcomes: Visceral Fascial Therapy showed effectiveness in reducing pain in patients with low back pain when combined with standard physical therapy, and in reducing gastroesophageal reflux symptoms in the short term. Limitations: High risk of bias. Low quality of the studies. The heterogeneity in study designs and methodologies may limit the generalizability of the findings. The evidence for the effectiveness of Fascial Therapy targeting visceral dysfunctions remains insufficient to support widespread clinical use.
Ceballos-Laita et al. (2024) [56]	Systematic review and meta-analysis	Craniosacral therapy	Various disorders	Outcomes: CST produced no statistically significant or clinically relevant changes in pain or disability for musculoskeletal disorders like headache, neck pain, low back pain, pelvic girdle pain, and fibromyalgia. CST was also ineffective for non-musculoskeletal disorders like infant colic, cerebral palsy, and visual function deficits. Limitations: While the literature searches were thorough, it is impossible to ensure no relevant studies were missed. The inclusion of a wide range of diverse conditions complicates the interpretation of the results

				and weakens the strength of the conclusions. There was considerable heterogeneity across the included RCTs in terms of treatment duration and outcome variables, which may limit the validity of the quantitative syntheses.
Bonanno et al. (2024) [28]	Scoping review	Osteopathic manipulative treatment (OMT)	Healthy individuals and patients with chronic musculoskeletal pain	Outcomes: OMT appears to influence brain activity in healthy individuals and more significantly in patients with chronic musculoskeletal pain. The review includes studies involving fMRI, EEG, and brain connectivity analysis. Limitations: Limited number of included studies with mixed designs (RCTs, pilot studies, and crossover studies). Studies had variable methodologies and sample sizes. More high-quality RCTs are needed to confirm the findings on brain activity and neurophysiological effects of OMT.
Carrasco-Uribarren et al. (2024) [149]	Systematic review and meta-analysis	Craniosacral therapy	Patients with headache disorders	Outcomes: Craniosacral therapy resulted in a statistically significant but clinically unimportant change in pain intensity. No significant change in disability or headache effect . Very low certainty of evidence. Limitations: The evidence quality was downgraded to very low. Small number of studies (4 studies) with a limited sample size. Pain reduction was statistically significant but clinically irrelevant. No significant effects on disability or headache effect.
Farra et al. (2024) [76]	A comprehensive mapping review	Osteopathic manipulative treatment (OMT)	General population with various conditions	Outcomes: The review found biological effects induced by OMT,

				particularly neurophysiological and musculoskeletal changes. Limitations: Significant variability in study designs, participant conditions, OMT protocols, and documented biological effects. The diverse nature of the studies complicates the ability to draw definitive conclusions. The review suggests the need for further research to clarify whether these changes are specifically due to OMT and to corroborate their clinical implication.
Ceballos-Laita et al. (2024) [57]	Systematic review and meta-analysis	Visceral osteopathy	Patients with various musculoskeletal and non-musculoskeletal conditions	Outcomes: Visceral osteopathy showed no significant improvement in musculoskeletal conditions such as low back pain, neck pain, or urinary incontinence. No effect was found for non-musculoskeletal conditions like irritable bowel syndrome, breast cancer, or preterm infants. Studies had high risk of bias and low-to-very low certainty of evidence. Limitations: Most studies were at high risk of bias. Certainty of evidence was downgraded to low or very low. No statistically significant changes in outcomes. Positive results in non-musculoskeletal conditions were based on flawed studies. Many studies did not report adverse events.

Appendix C. Effects and Potential Mechanisms of Osteopathy and Chiropractic in Musculoskeletal Pain: Placebo Response: Interaction Between Non-Specific and Contextual Factors in Osteopathic and Chiropractic Practices for Musculoskeletal Care

Author (Year)	Study Type	Mechanism and Effect Placebo	Population	Outcomes and Limitations
Benedetti et al. (2005)[140]	Narrative review	Neurobiological mechanisms of placebo effect	General population	Outcomes: Identified several neurobiological mechanisms underlying placebo effects.

				Highlighted the role of opioid and non-opioid neurotransmitter systems in placebo analgesia. Described how placebo effects can modulate various physiological systems beyond pain, including motor performance and immune responses. Limitations: The complexity of placebo mechanisms makes it challenging to isolate specific factors. Many studies cited were conducted in experimental settings, which may not fully reflect clinical realities. The review doesnot address potential differences in placebo mechanisms across different medical conditions or populations.
Eippert (2009) [88]	Experimental	Descending modulation mechanisms in placebo analgesia	Healthy volunteers	Outcomes: Placebo analgesia is associated with increased activity in the dorsolateral prefrontal cortex, rostral anterior cingulate cortex, and periaqueductal gray matter. This activation was reversed by the opioid antagonist naloxone, indicating the involvement of endogenous opioids. The study provided indirect evidence that opioidergic descending pain control circuits underlie placebo analgesia. Limitations: Relatively small sample size. The study was conducted on healthy volunteers, which may limit generalizability to clinical pain conditions. The use of experimental pain may not fully reflect chronic pain experiences. The study focused on short-term effects and did not address long-term placebo responses.
Schweinhardt et al. (2009) [89]	Experimental	Placebo analgesia and personality traits	Healthy volunteers	Outcomes: The study suggests that the anatomy of the mesolimbic reward system may predispose individuals to placebo analgesia. Found a correlation between placebo analgesic responses and gray matter density in the mesolimbic reward system: ventral striatum, insula, and medial prefrontal cortex. Identified a link between placebo analgesia and personality traits: ego-resiliency and straightforwardness. Limitations: Small sample size limits generalizability.

				The study was conducted on healthy volunteers, which may not reflect responses in clinical pain populations. The correlational nature of the findings limits causal inferences. The study focused on brain structure rather than function, which may not capture the full complexity of placebo responses.
Hróbjartsson, Gøtzsche (2010) [91]	Systematic review and meta-analysis	Placebo interventions for all clinical conditions	Patients with various clinical conditions	Outcomes: Found no evidence that placebo interventions have important clinical effects in general. Possible small benefits in studies with continuous subjective outcomes and for the treatment of pain. In general, no significant effects outcomes. Limitations: High heterogeneity among studies. Difficulty in distinguishing genuine placebo effects from bias. Lack of data on harms of placebo interventions.
Stein et al. (2012) [146]	Experimental	White matter integrity and placebo analgesia	Healthy volunteers	Outcomes: Found that white matter integrity of the descending pain modulatory system, particularly in the dorsolateral prefrontal cortex and rostral anterior cingulate cortex, predicted individual differences in placebo analgesia. Suggests a neuroanatomical basis for variability in placebo responses. Limitations: Small sample size. Study conducted on healthy volunteers, limiting generalizability to clinical populations. Focus on acute experimental pain may not reflect chronic pain conditions.
Amanzio (2013) [142]	Meta-analysis	Brain connectivity in placebo analgesia	Healthy volunteers	Outcomes: Identified consistent activation patterns associated with placebo analgesia, including in the rCCA, CPFDL, and PAG. Deactivation was observed in areas processing pain. The study supports the involvement of opioid and non-opioid mechanisms in placebo analgesia. Limitations: Focus on experimental pain in healthy volunteers may limit generalizability to clinical pain. Heterogeneity in study designs and analysis methods across included studies.

				The meta-analysis was based on a relatively small number of neuroimaging studies
Atlas, Wager (2014) [141]	Meta-analysis	Placebo analgesia and expectancy-based pain modulation	Healthy volunteers	Outcomes: Consistent placebo-induced reductions in pain-related brain regions (dorsal anterior cingulate, thalamus, insula, amygdala, striatum) Increased activation in prefrontal cortex, midbrain, and rCCA. Suggests placebo effects impact both pain processing and emotion/value systems. Limitations: Variability in experimental designs across studies. Focus on contrasts rather than correlations with behavior. Limited ability to determine causal mechanisms.
Büchel (2014) [145]	Perspective/Review	Placebo hypoalgesia and predictive coding	N/A (Not applicable)	Outcomes: Proposes a hierarchical Bayesian framework based on predictive coding to explain placebo hypoalgesia. Suggests that placebo hypoalgesia results from combining top-down prior expectations with bottom-up sensory signals. Emphasizes the importance of both the mean and precision of predictions and sensory signals. Reframes the ascending and descending pain systems as a recurrent system implementing predictive coding. Limitations: Conceptual framework, not an empirical study. Focuses only on acute pain in healthy individuals. Precise neurobiological implementation of the model remains speculative.
Colloca (2014) [78]	Narrative review	Placebo and nocebo responses in pain management	General population	Outcomes: The paper synthesizes mechanisms behind placebo and nocebo effects, particularly in pain management, highlighting the role of cognitive, emotional, and contextual factors in modulating pain perception. Neurobiological pathways (e.g., endogenous opioids, dopamine) are explored. Limitations: The study is a synthesis, lacking direct empirical data. It heavily relies on secondary sources, which may introduce bias in interpretation.

				The generalizability of findings across diverse clinical scenarios remains uncertain.
Peciña, Zubieta (2014) [139]	Narrative review	Molecular mechanisms of placebo responses in humans	Patients with various clinical conditions	Outcomes: The study investigates the role of the μ-opioid receptor system in mediating placebo analgesia. It identifies specific neurobiological pathways, showing that placebo effects are influenced by the brain's pain and reward modulation systems. The interaction between dopamine and opioid pathways is highlighted in placebo responses. Limitations: This is a review paper, so it is based on secondary data and may be biased. Further research is needed to explore these mechanisms in diverse clinical populations.
Wager, Atlas (2015) [94]	Review	Neuroscience of placebo effects, focusing on context, learning, and health	General population	Outcomes: The review explores neural mechanisms of placebo effects, highlighting the role of the prefrontal cortex, endogenous opioid and dopamine pathways, and the influence of learning and context on treatment outcomes. Limitations: Lacks new empirical data and focuses broadly on neuroscience, limiting its applicability to specific clinical contexts like musculoskeletal care. Further research is needed to validate these mechanisms in diverse settings.
Cerritelli (2016) [132]	Systematic Review	Placebo/sham therapy in osteopathy	Healthy population and population with different clinical conditions.	Outcomes: Evaluation of the application of placebo and sham therapies in osteopathic clinical trials. The lack of standardized methods and variability in sham approaches across studies are highlighted. High heterogeneity in the design of placebo controls, making clear conclusions on the effectiveness of sham therapies difficult. Limitations: High risk of bias in studies, particularly in allocation, blinding and selective reporting. Variation in sham therapy methodologies and insufficient reported information make it difficult to assess placebo effects in osteopathy. A quantitative analysis could not be performed due to these methodological limitations. The article highlights the need to develop standardized guidelines for placebo controls in manual medicine trials.

Testa, Rossettini (2016) [83]	Narrative review	Placebo and nocebo effects in physiotherapy	General population undergoing physiotherapy	Outcomes: The review examines the neurobiology of placebo and nocebo effects in physiotherapy. It highlights the role of contextual factors, such as the physiotherapist's and patient's characteristics, the therapist–patient relationship, and the healthcare environment. Contextual factors are identified as key modulators of clinical outcomes. Focus is placed on enhancing placebo effects and minimizing nocebo effects in physiotherapy treatments. Limitations: The review is a narrative synthesis, relying on existing literature without new empirical data. It centers on general placebo and nocebo concepts but lacks specific experimental evidence. The clinical applicability of the discussed effects in physiotherapy remains unvalidated through direct experimentation.
Ashar (2017) [92]	Narrative review	Placebo mechanisms and affective appraisal	Not specified	Outcomes: This review provides an overview of the placebo effect and its underlying brain mechanisms, particularly how appraisals of treatments influence outcomes. It identifies how placebo treatments, including those for pain, engage a core network of brain regions associated with self-evaluation, emotion, and reward processing, within the default mode network. The review emphasizes that placebo effects work by modifying how people evaluate their symptoms and future well-being. Limitations: The review does not introduce new empirical data or clinical trials. The generality of the findings, based on cognitive and neural appraisals, limits its direct applicability to specific clinical conditions or populations.
Beedie et al. (2018) [93]	Editorial	The role of placebo effects in CAM use in sports medicine and physiotherapy	Athletes and practitioners (elite and non-elite)	Outcomes: This review discusses the role of placebo and nocebo effects in complementary and alternative medicine (CAM) in sports medicine, emphasizing the complexity and variability of placebo effects. It presents placebo mechanisms like dopamine and opioid systems. Highlights challenges in using placebo effects to legitimize CAM, including variability,

				negative placebo effects (nocebo), and ethical concerns around deception. Suggests "headroom" mechanisms: the capacity to respond to placebos could indicate reserve capacity for legitimate treatments. Limitations: The review is based on existing literature and lacks original empirical data. Limited to placebo mechanisms, not addressing the full spectrum of CAM effects or evidence. Caveats in using placebo mechanisms for CAM are not fully explored, especially with regards to practical application in sports physiotherapy. Some recommendations may not be directly applicable across all CAM practices.
Blasini et al. (2018) [82]	Narrative review	The role of patient-practitioner relationships in placebo and nocebo phenomena	Pain patients (general clinical setting)	Outcomes: Identifies the biopsychosocial factors influencing placebo and nocebo effects in the patient-practitioner relationship. Emphasizes the role of expectancies and contextual factors (verbal suggestions, conditioning, and social observation) in shaping therapeutic outcomes. Found that macro (cultural, societal) and micro (individual psychobiological traits) factors influence expectancies. Empathy, friendliness, and competence of the practitioner enhance positive expectancies and placebo effects. Patient-practitioner caring and warm interactions improve the therapeutic experience, particularly for pain patients. Limitations: The review is based on existing literature without new empirical data. Focuses on theoretical models, lacking direct experimental evidence in the clinical setting. Subjective interpretations and lack of systematic analysis may reduce generalizability of findings across different clinical populations. The review does not provide concrete guidelines for integrating these findings into clinical practice.
Cai, He (2019) [137]	Narrative review	Placebo effects and molecular biological components involved	General clinical setting	Outcomes: Summarizes the history and characteristics of placebo effects. Identifies key molecular components involved in placebo effects, including the

				dopamine, opioid, serotonin, and endocannabinoid systems. Introduces the concept of placebome, aiming to understand the genetic and molecular basis of placebo effects. Discusses placebome studies and the need for no-treatment control (NTC) to identify genetic targets. Limitations: The placebome concept is still in its early stages. Lacks experimental data and new empirical findings. No clinical trials were included to test the molecular findings in real clinical settings. Emphasizes theoretical bioinformatics analysis rather than practical evidence in the clinical context. Need for NTC-controlled placebo studies to validate results and further explore the genetic targets related to placebo effects.
Anderson, Stebbins (2020) [80]	Narrative review	Determinants of placebo effects and responses	General clinical and research settings	Outcomes: Explores intrinsic factors influencing placebo responses, including patient expectations, previous experiences, neural systems under treatment, personality traits, and situational factors. Identifies clinician determinants, such as empathy, perceived expertise, clinical relationship quality, and belief in treatment efficacy. Analyzes extrinsic factors, such as study design, advertising, branding, and cultural influences, highlighting their combined impact on placebo effects. Limitations: Provides a theoretical framework without new empirical evidence. Focuses on general determinants of placebo effects rather than specific contexts, such as musculoskeletal care. Does not evaluate how identified factors quantitatively influence placebo responses in clinical practice or research.
Crawford et al. (2021) [144]	Experimental study	Brainstem mechanisms involved in placebo analgesia and nocebo hyperalgesia	Healthy volunteers	Outcomes: Found altered activity in key pain modulatory brainstem nuclei during placebo and nocebo responses. Identified distinct recruitment of the PAG-RVM pathway during greater placebo analgesia and nocebo hyperalgesia.

				Demonstrated differential activation of the parabrachial nucleus and overlapping activation in the substantia nigra and locus coeruleus for both effects.
				Suggests that the PAG-RVM pathway influences pain modulation at the level of the dorsal horn.
				Limitations:
				Small sample size (N = 25) limits generalizability of findings. Study focuses on acute experimental pain, reducing relevance to chronic pain scenarios.
				Deceptive conditioning may introduce variability in participants◎responses.
				Findings are correlational, limiting causal inference about brainstem circuitry and pain modulation.
Shi et al. (2021) [79]	Experimental study	Placebo and nocebo responses in acute lower back pain (ALBP)	Healthy volunteers	Outcomes:
				Significant differences in VAS pain scores observed for placebo and nocebo interventions compared to baseline and between placebo and nocebo groups.
				Placebo network involves negative lagged-temporal correlation between the DLPFC, secondary somatosensory cortex, ACC, and IC.
				Positive correlations were found between IC, thalamus, ACC, and SMA.
				Nocebo network includes positive correlations among primary somatosensory cortex, caudate, DLPFC, and SMA.
				Placebo response engages the reward system, inhibits the pain network, and activates opioid-mediated analgesia and emotion pathways.
				Nocebo response deactivates emotional control and primarily engages pain-related pathways.
				Verified that placebo and nocebo networks share brain regions but also have distinct features.
				Limitations:
				Small sample size (N = 20) limits the generalizability of findings.
				Study was conducted in healthy individuals, which may not reflect responses in clinical populations with chronic pain.
				Correlational nature of findings limits causal interpretations.
				fMRI-based GCA may be influenced by methodological biases, such as signal variability and lag-time estimation.
			N/A	Outcomes:

Thomson et al. (2021) [95]	Editorial/review	Exploration of contextual factors (CFs) in osteopathy and musculoskeletal care		Highlights the critical role of contextual factors such as clinician habits, patient expectations, therapeutic relationships, and treatment environments in shaping clinical outcomes. Suggests CFs influence outcomes via placebo and nocebo effects. Discusses the lack of CF awareness in osteopathic education and its implications for enhancing patient outcomes. Proposes research directions for better integration and evaluation of CFs in osteopathy and healthcare. Limitations: The study is narrative and does not include new empirical data or quantitative analysis. Limited generalizability due to its focus on osteopathy, though findings may apply broadly. Recommendations are theoretical and require further research validation through robust empirical methods. Does not specify direct evidence linking CF manipulation to improved outcomes in osteopathy.
Zunhammer et al. (2021) [148]	Systematic meta-analysis	Neural systems and brain mechanisms underlying placebo analgesia, based on experimental fMRI studies	Healthy volunteers	Outcomes: Identifies placebo analgesia as a multifaceted phenomenon involving multiple brain areas, including ventral attention networks (mid-insula), somatomotor networks (posterior insula), thalamus, habenula, mid-cingulate cortex, and supplementary motor area. Behavioral placebo analgesia correlates with reduced pain-related activity and increased frontoparietal activity, highlighting mechanisms of nociception, affect, and decision-making in pain. Significant between-study heterogeneity suggests variability in cerebral mechanisms across studies. Limitations: High between-study heterogeneity limits the ability to generalize findings across placebo analgesia contexts. Focuses on healthy participants; results may not directly translate to clinical populations with chronic pain. While robust at the neural level, behavioral and psychological interpretations of findings are limited.

				Excluded eight eligible studies due to lack of participant-level data, potentially introducing selection bias.
Bieniek, Bąbel (2023) [86]	Experimental study	Placebo hypoalgesia induced through operant conditioning using verbal, social, and token-based rewards and punishers	Healthy volunteers	Outcomes: Placebo hypoalgesia was successfully induced in groups with social and token-based reinforcement, but not with verbal reinforcement alone. Expectations of pain mediated the hypoalgesic effect, suggesting cognitive involvement. The number of reinforcers received predicted the magnitude of hypoalgesia, highlighting the role of conditioning intensity. Findings suggest token-based and social consequences may optimize pain management interventions. Limitations: Focused on healthy participants, limiting generalizability to clinical populations with chronic pain. Did not evaluate the long-term stability of placebo hypoalgesia effects. The study lacked diversity in participant demographics, potentially influencing the broader applicability of findings. While results highlight conditioning effects, their translation to clinical practice requires further investigation.
Testa et al. (2023) [84]	Book chapter/review	Management of cognitive, relational, and environmental contextual factors to optimize placebo effects and minimize nocebo effects in clinical practice	General population	Outcomes: Contextual factors, including beliefs, expectations, and therapeutic relationships, significantly enhance the outcomes of evidence-based treatments. Effective management of negative mindsets through empathic relationships can improve patient experience. Clinician's attitude and skills in addressing contextual effects add measurable value to the therapeutic process. Limitations: The review provides theoretical guidance but lacks empirical validation of specific strategies for managing contextual factors. Generalized conclusions may not apply across all patient populations or clinical settings. Limited discussion of practical implementation challenges in clinical practice.
			General population	Outcomes:

				Cultural beliefs, norms, and values shape treatment expectations and responses to placebo and nocebo effects.
				Physical and aesthetic preferences, influenced by culture, affect the perceived efficacy of treatments.
				Spiritual and religious beliefs impact coping strategies and treatment responses.
Colloca et al. (2023) [85]	Book chapter/review	Cultural influences on placebo and nocebo responses, including beliefs, rituals, and healthcare relationships		Rituals and healthcare provider-patient dynamics (e.g., verbal and nonverbal cues) are critical in shaping placebo/nocebo responses.
				Limitations:
				The review is theoretical and lacks empirical data directly validating the role of cultural factors in placebo/nocebo responses.
				Generalizations are based on broad cultural concepts, which may not capture specific individual or subgroup variations.
				Limited exploration of how cultural factors interact with biological or psychological mechanisms.
				Outcomes:
				No significant differences in gamma-aminobutyric acid (GABA) or other metabolites between placebo responders and non-responders in the right DLPFC.
				Identified an inverse relationship between glutamate levels and pain rating variability during conditioning.
				Demonstrated altered functional connectivity between the DLPFC and midbrain periaqueductal gray (PAG) during placebo analgesia.
Crawford et al. (2023) [144]	Experimental study	Brain mechanisms of placebo analgesia	Healthy volunteers	Highlighted the role of the DLPFC in shaping stimulus-response relationships during conditioning.
				Limitations:
				The study was conducted on healthy individuals, limiting its applicability to clinical populations.
				The small sample size (38 participants) reduces the generalizability of findings.
				The study focuses only on acute pain scenarios, limiting its relevance to chronic pain contexts.
				Correlational nature of findings does not establish causation between DLPFC activity and placebo response.
Hartmann et al. (2023) [81]	Experimental study	Empathy-related psychological and structural brain	Healthy volunteers	Outcomes:
				Placebo analgesia responders exhibited higher helping behavior and lower

		differences between placebo analgesia responders and non-responders		psychopathic traits compared to non-responders. Responders showed greater pain-related empathic concern. Structural brain differences: non-responders had increased gray matter volume in areas like the left inferior temporal and parietal supramarginal cortical regions and increased cortical surface area in the bilateral middle temporal cortex. Limitations: Uncorrected results in some analyses may lead to overestimated conclusions. Focus on a relatively narrow trait-based classification (e.g., empathy, psychopathy) without comprehensive exploration of other individual differences. Study paradigm and setting could influence outcomes, suggesting that contextual factors were not fully controlled for.
Meeuwis et al. (2023) [87]	Systematic Review and Meta-analysis	The effect of observational learning on placebo hypoalgesia and nocebo hyperalgesia	Healthy volunteers	Outcomes: Invest Observational learning (OL) had a small-to-medium effect on pain ratings (SMD = 0.44). - OL had a large effect on pain expectancy (SMD = 1.11). Empathic concern of the observer was positively correlated with the magnitude of placebo/nocebo effects (r = 0.14). Type of observation (in-person vs. videotaped) influenced the effect size ($p < 0.01$). Limitations: Moderate heterogeneity across studies. No clear clinical application of findings in chronic pain populations. Lack of placebo type modulation in the results (P = 0.23), suggesting further research is needed to clarify its role. Limited exploration of other empathy-related factors beyond empathic concern.
Rossettini et al. (2023) [138]	State of the art review	Overview of placebo and nocebo effects in experimental and chronic pain	Healthy volunteers and chronic pain patients	Outcomes: Strong evidence that placebo and nocebo effects are influenced by the psychosocial context. Psychological mechanisms and neurobiological/genetic determinants of placebo and nocebo effects are detailed. Differences in the occurrence of these effects between experimental settings (healthy participants) and clinical settings (chronic pain patients).

				Emphasizes the heterogeneity of pain in chronic patients affecting the magnitude of these effects. Limitations: Heterogeneity of pain in chronic patients makes results difficult to generalize. No unified results on the magnitude and occurrence of placebo/nocebo effects in chronic pain patients. Lacks specific experimental data to validate the proposed mechanisms in clinical settings. Calls for future research to address these gaps and improve the understanding of contextual factors.
Caliskan et al. (2024) [97]	Clinical update Review	Focus on treatment expectations, placebo/nocebo effects, and contextual factors	Patients in clinical settings, with an emphasis on pain management	Outcomes: Treatment expectations significantly influence treatment outcomes, acting as powerful modulators of health outcomes. Contextual factors that modify expectations can improve therapy success. Placebo analgesia and nocebo hyperalgesia are key mechanisms in the management of pain, with the expectations contributing to the overall treatment success. Further research is needed to personalize treatment strategies based on individual patient expectations. Limitations: The article is a clinical update and relies on existing evidence, with limited experimental data. It discusses variability in placebo/nocebo responses but does not identify clear predictors for individual responses. Calls for future research to explore personalized approaches to modulating treatment expectations. Does not address all clinical conditions in depth beyond pain.
Pedersen et al. (2024) [96]	Systematic review and meta-analysis	Focus on placebo effects, specific treatment effects, and changes observed without treatment in interventions for chronic nonspecific low back pain (NSLBP)	Adults with chronic nonspecific low back pain (NSLBP)	Outcomes: Approximately half of the overall treatment effect in conservative interventions for chronic NSLBP is attributed to changes observed without treatment, with smaller contributions from specific treatment and placebo effects. For pain intensity, 33% is attributed to specific treatment effects, 18% to placebo effects, and 49% to no-treatment changes.

				For physical function and HRQoL, 53% and 48% of the effect, respectively, is due to no treatment changes. Limitations: Low certainty of evidence, suggesting that the true effects might differ significantly from the reported estimates. The study is focused on conservative and passive interventions, which limits the applicability to other treatment types. The findings are based on short-term treatment effects and may not reflect long-term outcomes.
Saueressig et al. (2024) [46]	Review and methodological analysis	Focus on the methods used to quantify contextual effects in clinical care, particularly in placebo-controlled studies	N/A	Outcomes: The study critiques existing methods for quantifying contextual effects and proposes that the most effective method is comparing a placebo group with a non-treated control group. Other methods (such as the placebo control arm alone or proportional contextual effect calculation) are deemed inappropriate. This paper aims to provide guidance on best practices for estimating contextual effects in clinical research. Limitations: The review lacks empirical data as it is a methodological analysis, meaning it does not directly address clinical outcomes or interventions. It focuses only on theoretical frameworks and does not provide practical examples or real-world clinical applications. The effectiveness of the proposed method has not been fully tested or validated in diverse clinical settings.

Appendix D. Effects and Potential Mechanisms of Osteopathy and Chiropractic in Musculoskeletal Pain: Cognitive-Mediated Effects and Bias in Osteopathic and Chiropractic Practices for Musculoskeletal Care

Author (Year)	Study Type	Psychological elements of the CAMs	Population	Outcomes and Limitations
Forer (1949) [115]	Experimental	Personal validation fallacy	College students	Outcomes: Demonstrated how people tend to accept vague, general personality descriptions as accurate. Limitations: Limited sample, potential experimenter bias.
	Review			Outcomes:

Beyerstein (2001) [124]		Reasoning errors in alternative medicine	General population	Identified common logical fallacies in CAM beliefs. Limitations: Lack of empirical data.
Kaptchuk (2002) [116]	Review	Placebo effect in CAM	General population	Outcomes: Discussed potential clinical significance of healing rituals. Limitations: Lack of original data.
Winslow, Shapiro (2002) [108]	Cross-sectional survey	Physicians◎attitudes towards CAM education	American physicians	Outcomes: Physicians want more CAM education to better communicate with patients. Limitations: Potential response bias.
Klein, Helweg-Larsen (2002) [111]	Meta-analysis	Perceived control and optimistic bias	General population	Outcomes: Positive correlation between perceived control and optimistic bias. Limitations: Heterogeneity in included studies. The findings may not be generalizable to the use of CAM.
Honda et al. (2005) [99]	Cross-sectional survey	Personality, coping strategies, and social support in CAM use	American adults	Outcomes: Personality traits, coping strategies and social support influence CAM use. Limitations: Self-reported data, potential recall bias.
Singh et al. (2005) [113]	Qualitative study is based on in-person interviews	Motivation for CAM use	Men with prostate cancer	Outcomes: Identified various motivations for CAM use, including hope and empowerment. Limitations: Small sample size. Limited generalizability to musculoskeletal care.
Shih et al. (2009) [114]	Cross-sectional survey	CAM usage patterns	Singaporean adult cancer patients	Outcomes: High prevalence of CAM use, influenced by cultural factors. Limitations: Single-center study. Potential selection bias. Limited generalizability to musculoskeletal care.
Sperber (2010) [120]	Theoretical review	The “Guru Effect” in alternative beliefs	N/A	Outcomes: Proposed mechanism for why people trust incomprehensible ideas from perceived authorities. Limitations: Lack of empirical testing.
				Outcomes:

				Patients showed improved outcomes during the screening process before receiving any treatment. This effect led to an overestimation of treatment efficacy in clinical trials.
Wolfe, Michaud (2010) [122]	Observational study	Hawthorne effect in clinical trials	Patients with rheumatoid arthritis (RA)	Limitations: Study based on observational data, which may limit causal inferences. Potential confounders are not fully controlled. Generalizability to other conditions or trial designs may be limited.
Berthelot et al. (2011) [121]	Commentary	Hawthorne effect vs placebo effect	N/A	Outcomes: Argued Hawthorne effect may be stronger than placebo in some cases. Limitations: Limited empirical evidence presented.
Walach (2013) [90]	Book chapter/review	Placebo effects in CAM	General population	Outcomes: Discusses the role of placebo effects in CAM, suggesting that these effects may be particularly strong in CAM due to the holistic approach and strong therapeutic relationships. Proposes that CAM might trigger self-healing responses through various contextual and psychological factors. Limitations: Not peer-reviewed research. May lack the rigorous methodology of a systematic review or meta-analysis. The generalizability of the conclusions may be limited due to the diverse nature of CAM practices.
Benedetti et al. (2013) [98]	Experimental	Pain perception and opioid/cannabinoid systems	Healthy volunteers	Outcomes: Changing pain meaning from negative to positive activates opioid and cannabinoid systems. Limitations: Small sample size. laboratory setting.
Yarritu, Matute (2015) [104]	Experimental	Causal illusion in health beliefs	University students	Outcomes: Prior knowledge can induce an illusion of causality through biased behavior. Limitations: Artificial laboratory task.
		Cognitive bias		Outcomes:

Blanco (2017) [102]	Book chapter/Review		General population	Defined and described various cognitive biases. Limitations: Not original research. Not peer-reviewed research.
Stub et al. (2017) [118]	Qualitative interviews	Complementary therapists' reflections on practice	Norwegian CAM practitioners	Outcomes: Therapists often refer to "patient healing power" as placebo effect. Limitations: Small sample. Potential social desirability bias.
Galbraith et al. (2018) [112]	Systematic review	Traits and cognitions associated with CAM use/belief	CAMs user	Outcomes: Identified personality traits and cognitive styles linked to CAM use. Limitations: Heterogeneity in included studies.
Garrett et al. (2019) [119]	Mixed methods	Perceptions of internet-based health scams	UK adults	Outcomes: Identified factors promoting engagement with online health scams. Limitations: Potential selection bias in online sample.
Moreno Castro et al. (2019) [101]	Qualitative research methods	Influences on perception of pseudo-therapies	Spanish population	Outcomes: Media, social circles, and education influence pseudo-therapy beliefs. Limitations: Self-reported data, potential social desirability bias.
Chow et al. (2021) [105]	Experimental	Causal relationships in pseudoscientific health beliefs	University students	Outcomes: Perceived frequency of causal relationships influences pseudoscientific beliefs. Limitations: Artificial laboratory task.
Rodríguez-Ferreiro et al. (2021) [106]	Experimental	Evidential criteria in pseudoscience believers	Spanish adults	Outcomes: Pseudoscience believers have lower evidential criteria. Limitations: The online sample may not be representative of the general population. Self-reported measurements may be subject to bias. The study's correlational nature limits causal inferences about the relationship between evidential criteria and pseudoscientific beliefs.
Davies et al. (2022) [117]	Systematic review	Knowledge used in CAM consultations	Physicians and patients	Outcomes: Classified types of knowledge used in CAM practice. Limitations:

				Heterogeneity in included studies.
Esteves et al. (2022) [100]	Theoretical paper	Osteopathic care as enactive inference	General population	Outcomes: Proposed theoretical framework for osteopathic practice. Limitations: Lack of empirical testing.
Garcia-Arch et al. (2022) [107]	Experimental	Expert feedback on pseudoscientific beliefs	Spanish adults	Outcomes: Expert feedback can increase acceptance of health-related pseudoscientific beliefs. Limitations: Online sample. Artificial task.
García-Arch et al. (2022) [109]	Correlational	Prediction of pseudoscience acceptance	Spanish adults	Outcomes: Information interpretation and individual differences predict pseudoscience acceptance. Limitations: Cross-sectional design, self-reported data.
Piñeiro Pérez et al. (2022) [110]	Cross-sectional survey	Pediatricians◎knowledge and use of CAM	Spanish pediatricians	Outcomes: Identified gaps in CAM knowledge among pediatricians. Limitations: Potential response bias.
Segovia et al. (2022) [9]	Cross-sectional survey	Trust and belief in pseudotherapies	Spanish adults	Outcomes: Pseudotherapy use is associated with trust in efficacy rather than belief in scientific validity. Limitations: Self-reported data. Potential social desirability bias.
Torres et al. (2022) [103]	Experimental	Causal illusion in pseudoscientific beliefs	Spanish university students	Outcomes: Information interpretation and search strategies influence causal illusions. Limitations: It does not allow us to know the causality between the illusions of causality and the tendency to maintain unjustified beliefs. There may be variables that are not controlled.
Vicente et al. (2023) [125]	Experimental	Prior beliefs◎influence on judgments of medicine effectiveness	University students	Outcomes: Prior beliefs influence judgments about both alternative and scientific medicine. Limitations: The online sample may not be representative, which prevents generalization of the results. Potential social desirability bias.

				The correlational nature of the study limits causal inferences. The study is based on hypothetical scenarios, which may not fully reflect how people would make decisions in real health situations. The study cannot fully control for other factors that might influence judgments about the effectiveness of treatments.
Neogi, Colloca (2023) [123]	Narrative review	Placebo effects in osteoarthritis	Patients with osteoarthritis	Outcomes: Placebo effects contribute significantly to pain relief in osteoarthritis. These effects are mediated by psychological factors and neurobiological mechanisms. Placebo responses may be enhanced by several factors, including the therapeutic encounter, treatment characteristics, and individual patient factors. It is suggested that understanding and harnessing placebo effects could improve clinical outcomes and drug development in osteoarthritis. Limitations: The review is based on existing literature, which may have variable quality and methodologies. Generalizability of the findings to all patients with osteoarthritis may be limited. The review does not provide new empirical data. The long-term effects of placebo responses in osteoarthritis are not well established.

Appendix E. Effects and Potential Mechanisms of Osteopathy and Chiropractic in Musculoskeletal Pain: The Effects Mediated by Context in Osteopathic and Chiropractic Practices for Musculoskeletal Care

Author (Year)	Study Type	Intervention/Contextual Focus	Population	Outcomes and Limitations
Kaptchuk (2002) [116]	Narrative review	Placebo Effect in CAM	General population	Outcomes: Discusses how ritualistic and symbolic aspects of alternative medicine can evoke clinically significant placebo responses. Limitations: Primarily theoretical; lacks empirical data to substantiate claims.

Paterson (2005) [133]	Narrative review	Placebo effect in acupuncture	Acupuncture patients	Outcomes: Distinguishes between characteristic and incidental (placebo) effects in acupuncture efficacy. Limitations: Lacks experimental data, limited generalizability beyond acupuncture.
Linde et al. (2005) [134]	Randomized Controlled Trial	Acupuncture	Migraine patients	Outcomes: The possible benefits of acupuncture may be due to factors other than those derived from the needling. Limitations: Lack of significant difference with control group suggests influence of non-specific factors.
Diener et al. (2006) [135]	RCT	Acupuncture	Migraine patients	Outcomes: Treatment outcomes for migraine did not differ significantly between verum acupuncture, sham acupuncture, and standard therapy groups, suggesting a strong influence of contextual factors Limitations: High dropout rate in the standard therapy group (106 patients) may have affected group comparability. Inability to blind participants to standard drug therapy could have influenced patient-reported outcomes. The study design did not allow for isolation of specific contextual factors from overall treatment effects.
Fulda et al. (2007) [128]	Pilot study	Osteopathic Manipulative Treatment (OMT)	Low back pain patients	Outcomes: Positive expectations can influence perceived efficacy, even in placebo treatments. Limitations: Small sample size limits generalizability; preliminary findings lack statistical power. Lack of control groups reduces the ability to isolate the impact of expectations.
Meissner et al. (2013) [130]	Systematic review	Placebo in migraine prophylaxis	Migraine patients	Outcomes: Efficacy among placebo treatments in preventing migraine. Limitations: Heterogeneity of included studies may affect consistency of conclusions.
Calpin et al. (2017) [127]	Comparative retrospective study.	Chronic pain management	Patients with chronic pain	Outcomes: Discrepancies in expectations were noted, with significant effects from patient characteristics like age, gender, and sleep quality on expectations. The study highlights the need to align expectations for better outcomes. Limitations:

				Small sample of physicians limits generalization. Based on descriptive comparisons only. Lack of follow-up after consultation. Possible misinterpretation of free responses.
Rossettini et al. (2018) [126]	Narrative review.	Placebo/nocebo in MSK care	Patients with musculoskeletal pain	Outcomes: Highlights influence of contextual factors on placebo and nocebo effects. Limitations: Lacks comprehensive analysis of primary data; broad generalizations may limit applicability.
Thomson et al. (2021) [95]	Clinical Commentary	Placebo/Contextual factors	General MSK care	Outcomes: Emphasizes the importance of contextual factors in enhancing treatment effects. Limitations: Lacks original data; primarily theoretical commentary.
Tsutsumi et al. (2023) [136]	Meta-epidemiological study	Contextual effects in general medicine	Data from Cochrane reviews	Outcomes: Estimates significant portion of medical treatment results attributable to contextual and placebo effects. Limitations: Focus on general medicine may limit direct applicability to musculoskeletal care.
Nim et al. (2025) [131]	Systematic review with network meta-analysis	Spinal manipulative therapy (SMT) application procedures	Adults with spine pain	Outcomes: Most SMT procedures were slightly more effective than other treatments; a general and non-specific SMT approach had the highest probability of achieving the largest effects. Limitations: Differences between SMT approaches were small and not clinically relevant; evidence was of low to very low certainty due to heterogeneity, bias, and lack of direct comparisons

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DISCUSIÓN

5 DISCUSIÓN

En la presente tesis doctoral se ha analizado de forma sistemática y crítica toda la evidencia disponible encontrada en las principales bases de datos biomédicas acerca de la efectividad clínica de la osteopatía y se ha distribuido la información en cuatro publicaciones diferentes.

La discusión global de estos resultados se ha dividido en dos apartados principales, uno acerca de la efectividad clínica y un segundo acerca de los efectos y potenciales mecanismos derivados de la osteopatía

5.1 EFECTIVIDAD CLÍNICA

Los resultados de las tres primeras revisiones sistemáticas con meta-análisis son:

- El análisis acerca de tratamiento holístico basado en el diagnóstico y tratamiento manual osteopático de manera pragmática en pacientes con dolor cervical y lumbar en las variables clínicas de intensidad de dolor, discapacidad y calidad de vida se ha mostrado que no muestra mejoras superiores a un placebo.
- El análisis acerca de la osteopatía visceral basada en el diagnóstico y tratamiento manual de las disfunciones viscerales encontradas en pacientes con dolor lumbar, dolor cervical, incontinencia urinaria, síndrome de colon irritable, cáncer de mama, nacimiento prematuro, reflujo gastroesofágico o síndrome de ovarios poliquísticos ha mostrado que no aporta cambios significativos en comparación con una técnica placebo, el tratamiento habitual o la ausencia de intervención.
- El análisis acerca de la osteopatía craneosacral o craneal basada en el diagnóstico y tratamiento manual de los huesos del cráneo o estructuras relacionadas con el mecanismo de respiración primario en pacientes con cefaleas, dolor de cuello, dolor lumbar, dolor pélvico, fibromialgia, cólico del lactante, nacimiento prematuro, trastorno de hiperactividad, parálisis cerebral o déficits visuales ha mostrado que no aporta mejoras estadísticamente significativas en comparación con técnicas placebo, el tratamiento habitual o la ausencia de intervención.

En referencia a la calidad y los sesgos metodológicos de los estudios incluidos, se debe destacar que de manera general el riesgo de sesgo presentado por la gran mayoría de los

estudios fue alto. El sesgo más frecuentemente detectado, pero no el único, entre todos los estudios analizados fue el sesgo de informe o de notificación. Esto es así ya que la mayoría de los estudios no habían publicado o registrado de manera previa el protocolo de los ensayos clínicos, había utilizado múltiples herramientas o formas de medición para objetivar las mismas variables o presentaban análisis estadísticos inadecuados en relación con los tamaños de la muestra, los intervalos de confianza, o el propio objetivo del estudio. Esto es de vital importancia ya que probablemente es el sesgo que más pueda afectar a los resultados del estudio. Además, también es importante destacar que, siempre que se pudo, se realizó una comparativa entre los estudios que presentaban menor y mayor riesgo de sesgo, mostrando de esta manera, una clara tendencia a la falta de resultados positivos en los estudios de mejor calidad, lo cual favorece la generalización de la falta de efectividad clínica de estas intervenciones.

Por último, es importante destacar la certeza de la evidencia obtenida a través de la cual podemos realizar una transferencia del conocimiento científico a la práctica basada en la evidencia. De forma general, para prácticamente la totalidad de las variables analizadas los autores tuvimos que degradar la certeza de la evidencia hasta baja o muy baja debido a la presencia de riesgo de sesgo, inconsistencias entre los parámetros evaluados, presencia de evidencias indirectas o imprecisiones debidas principalmente a los bajos tamaños muestrales incluidos. Según la interpretación llevada a cabo por los autores del propio instrumento, una evidencia baja significa que la confianza en el efecto estimado es limitada, pudiendo ser el efecto verdadero substancialmente diferente. Por su parte, la evidencia muy baja significa que la confianza en el efecto estimado es mínima, siendo probable que el efecto real sea substancialmente diferente.

Lógicamente, considerando en su conjunto los resultados obtenidos en las síntesis cualitativas y cuantitativas, los riesgos de sesgo observados, y la certeza de la evidencia analizada, se puede concluir que parece que la osteopatía no produce efectos positivos en ninguna de las variables ni patologías estudiadas, pero no de una manera firme. Esto es debido a que los estudios que se han llevado a cabo no presentan una calidad metodológica suficientemente alta como para que la certeza de la evidencia acompañe a la conclusión estadística de manera segura. Sin embargo, salvo en el caso de la osteopatía craneal en el cual parece existir más heterogeneidad, la evidencia disponible acerca de la osteopatía estructural y a la osteopatía visceral apunta en su gran mayoría a la misma dirección, la falta de efectividad clínica.

5.2 EFECTOS Y POTENCIALES MECANISMOS DERIVADOS DE LA OSTEOPATÍA

Los efectos globales de un tratamiento dependen de tres factores que interactúan entre sí como son los efectos específicos de una terapia, los efectos contextuales y los efectos no específicos. La suma de los factores contextuales y los no específicos es lo comúnmente conocido como respuesta placebo, basada principalmente en la percepción del paciente independientemente de que la intervención presente efectos específicos o no (Mamud-Meroni et al., 2025).

- **Efectos específicos**

Los efectos específicos pueden ser definidos como los cambios clínicos derivados de los mecanismos directos de la intervención. Actualmente la osteopatía no ha conseguido demostrar de manera clara ningún efecto específico (Carrasco-Uribarren et al., 2024; Ceballos-Laita, Ernst, Carrasco-Uribarren, Cabanillas-Barea, et al., 2024; Ceballos-Laita, Ernst, Carrasco-Uribarren, Esteban-Tarcaya, et al., 2024; Ceballos-Laita et al., 2023).

El contexto teórico de la osteopatía craneal o craneosacra se basa en la idea de que el cráneo está conectado con el sacro a través de las meninges y el líquido cefalorraquídeo formando un sistema dinámico. Bajo este pretexto, se asume que los huesos del cráneo presentan cierta capacidad de movimiento que impulsa y a su vez es impulsado por el líquido cefalorraquídeo causando cambios en las membranas durales y en la zona sacra. Hasta la fecha, no hay evidencia disponible que haga suponer de una movilidad de los huesos del cráneo. La evidencia actual expone que bajo condiciones normales los huesos del cráneo osifican completamente entre la edad de 13 y 18 años (Downey et al., 2006; Okamoto et al., 1996). Existen ciertos estudios que muestran movimientos milimétricos o incluso nanométricos de los huesos del cráneo (Bordoni & Escher, 2023), sin embargo, las habilidades palpatorias no permitirían discriminar estos movimientos (Ferguson, 2003). Por otro lado, la fiabilidad de la palpación del ritmo respiratorio primario no ha mostrado ser un método válido ni fiable de evaluación (Guillaud et al., 2016), sugiriendo que los movimientos que realmente se puedan sentir sean la respiración pulmonar o el ritmo cardíaco (Hidalgo et al., 2024).

El contexto teórico de la osteopatía visceral se basa en que la movilidad de las vísceras, bien por exceso o por defecto, crea patrones anormales de tensión e irritación crónica en

los tejidos circundantes que a su vez causan problemas funcionales y estructurales en todos los sistemas corporales como puede ser la alteración de la postura, la restricción de la movilidad articular, o la función neuromuscular (Barral & Mercier, 2004). Es correcto que la víscera presenta movimientos, y de hecho coincide con el movimiento respiratorio o con actividades tales como correr o saltar (Cazzola et al., 2014). Sin embargo, la idea de que la alteración de la movilidad de las vísceras pueda causar o agravar cualquier condición musculoesquelética o no musculoesquelética no se ha mostrado biológicamente plausible en la actualidad (Hidalgo et al., 2024). Además, la validez de las técnicas manuales palpatorias para localizar restricciones, tensiones, o malposiciones en las vísceras o tejidos fasciales asociados no ha mostrado ser fiable (Guillaud et al., 2018). Así como la idea de utilizar técnicas manuales y tener efecto desde las vísceras a otros tejidos como los músculos o las articulaciones porque existe una continuidad miofascial es una implausibilidad anatómica (Hidalgo et al., 2024).

En relación con la osteopatía estructural, la manipulación vertebral es probablemente la técnica más investigada y que ha mostrado cierta plausibilidad biológica. Se debe hacer un inciso en este apartado ya que la manipulación vertebral no corresponde de manera exclusiva a los osteópatas, y a que no todas las técnicas de manipulación son iguales.

En relación con la primera cuestión, quiroprácticos y fisioterapeutas también aplican este tipo de técnicas. Con respecto a la segunda cuestión, en la literatura se han encontrado las siguientes variantes de la manipulación vertebral: impulsos de alta velocidad y corta amplitud utilizando movimientos rotatorios o translatorios, en palanca corta o en palanca larga, en posición de reposo, posición media o posición máxima de la limitación del movimiento (Carrasco-Uribarren, Pardos-Aguilella, et al., 2022; Carrasco-Uribarren, Rodríguez-Sanz, et al., 2022; Cerritelli et al., 2015; G. V. Espí-López et al., 2016; G. V Espí-López et al., 2016; Malo-Urriés et al., 2017; Muñoz-Gómez et al., 2021; Rushton et al., 2015, 2023). Esta anotación es de vital importancia porque las manipulaciones osteopáticas, a pesar de haber demostrado ciertos efectos adversos, todos ellos han sido en su mayoría leves y transitorios. Sin embargo, las manipulaciones vertebrales utilizadas por quiroprácticos son las que más efectos adversos muestran habiéndose demostrados algunos de ellos muy graves (Kranenburg et al., 2017).

Diversos autores han descrito que la manipulación vertebral puede aliviar el dolor a través de mecanismos neurofisiológicos a nivel periférico, y medular principalmente. A nivel periférico, parece reducir la actividad de citocinas proinflamatorias y el estrés oxidativo, lo

que podría mitigar la inflamación y la sensibilización periférica (Gevers-Montoro et al., 2021). A nivel medular, se cree que la manipulación vertebral induce una inhibición segmentaria, lo que disminuye la sumación temporal de las señales nociceptivas y, en consecuencia, atenúa los procesos de sensibilización central. Estos efectos se han observado en un aumento de los umbrales de presión del dolor en los dermatomas y miotomas correspondientes, así como en una reducción de la sensibilidad a los estímulos térmicos (Aspinall et al., 2019; Bishop et al., 2011; George et al., 2006).

Sin embargo, aunque la manipulación vertebral influye en estos parámetros neurofisiológicos, estos cambios a menudo no se correlacionan de manera consistente con mejoras en el dolor, u otras variables funcionales (Nim et al., 2020). Además, las vías inhibitorias descendentes pueden contribuir a la reducción de la percepción del dolor, pero aún no está claro si esto es un efecto específico de la manipulación vertebral o si se debe a factores contextuales o no específicos que se describen a continuación (Bialosky et al., 2018).

- **Factores y efectos contextuales**

Los factores contextuales se refieren a todos aquellos que tengan que ver con la interacción entre los pacientes y los terapeutas. Dentro de estos se incluyen: 1) el ambiente ,el cual hace referencia al espacio en el cual se va a producir la intervención (color, temperatura, olor, etc...) y el material utilizado para el tratamiento (antigüedad, valor económico, limpieza, etc...); 2) la calidad de la relación con el profesional, la cual hace referencia a la empatía mostrada por el profesional, el vocabulario utilizado, interpretación de ideas propias y de dudas del paciente, la presencia de una relación previa etc..; 3) las expectativas del paciente y la credibilidad del terapeuta; y 4) los rituales y elementos simbólicos asociados con el proceso de tratamiento.

Estos factores contextuales se encuentran generalmente relacionado con los siguientes sesgos:

- Sesgo de causalidad: cuando un resultado o beneficio es erróneamente atribuido a una acción específica (Rodríguez-Ferreiro & Barberia, 2021). Por ejemplo, algunos de los estudios incluidos realizan el reclutamiento a través de los pacientes de clínicas osteopáticas, lo que quiere decir que las personas acuden directamente a un centro osteopático y/o tienen experiencias positivas con estas intervenciones a pesar de no presentar efectos específicos.

- Sesgo de autoridad: es frecuente que cuando un paciente no tiene conocimiento suficiente acerca de un tema sanitario, se deja guiar por quien considera una persona de autoridad (Garcia-Arch et al., 2022). En el caso de la osteopatía, los conceptos y preceptos utilizados son altamente complicados de entender por su posibilismo anatómico y su relación filosófica, lo cual lo hace altamente susceptible a este sesgo.
- Sesgo de optimismo: tendencia a sobreestimar los beneficios y despreciar potenciales riesgos (Klein & Helweg-Larsen, 2002). Por ejemplo, el uso de la manipulación cervical de forma no razonada en trastornos no musculoesqueléticos como el cólico del lactante, que pude derivar en efectos adversos severos.
- Sesgo de control de la ilusión: se refiere a la creencia de que uno pude influir en los resultados más allá de su control (Galbraith et al., 2018; Klein & Helweg-Larsen, 2002). Entre los más comunes en la osteopatía es la ilusión de mover los huesos del cráneo fusionados o las vísceras malposicionadas e influir con ello en patologías tanto musculoesqueléticas como no musculoesqueléticas.
- Sesgo de confirmación: se refiere a interpretar de manera selectiva la información que se alinee con sus creencias preexistentes (García-Arch et al., 2022; Shih et al., 2009; Singh et al., 2005). En este caso, el posibilismo anatómico descrito para justificar cualquier tipo de intervención osteopática es un claro ejemplo.
- Efecto Barnum: se refiere a la exposición de conceptos vagos y genéricos que pueden interpretarse de manera específica y personalizada (Forer, 1949).
- Efecto Hawthorne: ocurre cuando los pacientes modifican su comportamiento porque saben que están siendo estudiados por personas especializadas (Davies et al., 2022; Kaptchuk, 2002; Stub et al., 2017). Esto puede hacer que reflejen unos cambios positivos que no existieron realmente por favorecer a los investigadores.

En este sentido, los resultados positivos mostrados por ciertos individuos durante la aplicación de intervenciones osteopáticas que no han mostrado evidencia científica sólida parecen estar más relacionadas con las características inherentes del proceso más que con la intervención en sí misma. A pesar de que es altamente complicado controlar los factores contextuales, la metodología expuesta en los estudios incluidos parece mostrar que estos factores han podido ser mediadores del efecto.

- **Factores y efectos no específicos**

Los factores no específicos pueden crear efectos relacionados tanto con la intervención osteopática como con las valorables evaluadas. Entre los principales factores no específicos se encuentran: la historia natural de la enfermedad y la regresión a la media (Saueressig et al., 2024).

Los estudios incluidos en cada una de las revisiones sistemáticas planteadas incluían pacientes con patología tanto musculoesquelética como no musculoesquelética muy variada. Debido a esta amplia gama y naturaleza de trastornos abordados por la osteopatía, es probable que muchos de ellos se resuelvan de manera espontánea por el propio curso natural de la enfermedad. De este mismo modo, existen patologías que se presentan mediante episodios, como puede ser el caso de la fibromialgia, del dolor cervical o del dolor lumbar, por lo que también es plausible que ciertos pacientes mejoraran simplemente por su regresión a la media tras periodos de pico de dolor.

A pesar de que estos factores existen y no son fácilmente controlables, la falta generalizada de un grupo control estable, así como la presencia de intervalos de confianza amplios en variables de autoevaluación por parte del paciente hacen más que evidente la presencia de estos factores en los estudios evaluados.

- **Interacción entre factores: respuesta placebo**

La interacción entre estos los factores contextuales y no específicos dan como resultado una respuesta placebo, la cual es definida como una respuesta terapéutica que aparece independientemente de la efectividad intrínseca de la propia intervención. Este fenómeno, como se ha mencionado en los apartados anteriores, vendrá modulado por lo referente al comportamiento, las emociones y la cognición.

Es consecuente destacar que esta respuesta placebo es inseparable de la práctica clínica diaria de los fisioterapeutas, pero también es importante no basar la práctica clínica en la utilización de terapias que dependen exclusivamente de la manipulación de estos factores contextuales y no específicos ya que son en gran medida variables e impredecibles, y pueden favorecer una respuesta placebo, pero también una respuesta nocebo en otros, creando un empeoramiento clínico del paciente. En este sentido, las respuestas nocebo pueden llevar al paciente a desarrollar la percepción errónea de un problema inexistente o poco verosímil, lo que puede derivar en una dependencia hacia terapias que carecen de eficacia comprobada. Esto se ha estudiado en un reciente estudio de Ezzavatar et al. (Ezzatvar et al., 2024) donde mostró que cerca de la mitad del tratamiento pasivo utilizado en pacientes con dolor lumbar crónico podía ser atribuido a esta serie de efectos.

Además, la utilización clínica de este tipo de terapias basadas en las respuestas placebo, como parece ser la osteopatía, resulta en una serie de dilemas éticos ya que puede suponer un riesgo directo (por ejemplo la manipulación cervical en un bebé o en una persona con patología vascular), riesgos indirectos (derivados del retraso o la evitación de aplicar un tratamiento que presente efectos específicos), daños emocionales o económicos (principalmente en personas de renta reducida), y gasto de recursos clínicos.

5.3 IMPLICACIÓN CLÍNICA

Tras la evaluación de la totalidad de ensayos clínicos encontrados en las principales bases de datos biomédicas acerca de la osteopatía se puede señalar su falta de plausibilidad biológica y de efectividad clínica al comparase con un placebo o con la evolución natural de la enfermedad. La credibilidad de los efectos positivos de la osteopatía parece esta arraigada en su asociación con la Fisioterapia y la práctica por parte de los fisioterapeutas, sin embargo, los posibles efectos derivados de su utilización parecen estar sobreestimados y más relacionados con los efectos contextuales y no específicos. Por este motivo, con la evidencia disponible, no se puede recomendar su uso para el tratamiento de patologías musculoesqueléticas y no musculoesqueléticas al menos de forma prioritaria o aislada.

Esta Tesis Doctoral destaca la relevancia de consolidar una base sólida de educación sanitaria tanto en la población general como en el colectivo profesional. El propósito no es únicamente reducir la falta de información entre los pacientes que reciben estas terapias, sino también contribuir a erradicar concepciones erróneas que, transmitidas y reforzadas culturalmente a lo largo del tiempo, se han arraigado en la sociedad. Asimismo, es fundamental que los profesionales sanitarios asuman una actitud consciente y ética en la interpretación y aplicación de los resultados de la investigación.

5.4 LIMITACIONES

La presente Tesis Doctoral presenta una serie de limitaciones en los estudios aportados. En primer lugar, a pesar de que se ha evaluado toda la evidencia encontrada en las principales bases de datos biomédicas y se hayan empleado todas las herramientas disponibles para el acceso al mayor número de artículos, no podemos estar absolutamente seguros de que existan otros estudios que cubrieran el objetivo de estudio

y que no hayan sido incluidos. En segundo lugar, la inclusión de una gran variedad de patologías tanto musculoesqueléticas como no musculoesqueléticas en cada una de las revisiones complica la interpretación de los resultados y pueden debilitar la fuerza de las conclusiones. En tercer lugar, a pesar de que se ha llevado una evaluación cualitativa y cuantitativa de los estudios, los ensayos clínicos primarios presentaban una heterogeneidad considerable en términos de duración de intervenciones y herramientas de medición de las variables dependientes. Todas estas limitaciones han podido pone en riesgo y limitar la validad del análisis cuantitativo principalmente.

CONCLUSIONES

6 CONCLUSIONES

1. Los hallazgos de una revisión sistemática con meta-análisis revelaron que la aplicación pragmática de la osteopatía estructural siguiendo sus propios procesos de evaluación basados en la palpación no muestra una mejora estadísticamente significativa al ser comparada con intervenciones placebo para pacientes con dolor lumbar o cervical.

2. Los hallazgos de una revisión sistemática con meta-análisis revelaron que la osteopatía visceral no produce ninguna mejora clínica para ninguna de las disfunciones musculoesqueléticos o no-musculoesqueléticos estudiadas.

3. Los hallazgos de una revisión sistemática con meta-análisis mostraron que la osteopatía craneal o craneosacra no es clínicamente efectiva para el tratamiento de ninguna de las disfunciones musculoesqueléticos o no-musculoesqueléticos estudiadas.

4. La evidencia actual no respalda el uso de la osteopatía como tratamientos de primera línea para las disfunciones musculoesqueléticas o no-musculoesqueléticas. Sus efectos parecen estar motivados por factores contextuales y no específicos (como las expectativas del paciente, el entorno del estudio, el tipo y momento de las intervenciones, así como efectos como el placebo, la regresión a la media y la evolución natural de la enfermedad), los cuales influyen en los resultados y limitan la validez y generalización de los hallazgos sobre su efectividad clínica.

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7 REFERENCIAS

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