Thesis

Association of Acupuncture Dosage to Acupuncture´s Analgesic Effect in Cancer-Related Pain

A Meta-Analysis and Meta-Regression of Acupuncture Randomized Controlled Trials

submitted by

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Zusammenfassung

Einleitung: Aktuelle Leitlinien empfehlen Akupunktur als integrative Therapieoption bei Tumorschmerzen. Die Wirkung und Wirkungsweise der Akupunktur werden zunehmend nach westlichen wissenschaftlichen Standards untersucht. Die Dosierung ist ein bisher noch wenig erforschter Faktor, der jedoch für die Genauigkeit der Forschungsergebnisse und für sozioökonomische Aspekte bei der Umsetzung des multimodalen Therapiekonzeptes von Bedeutung ist. Ziel dieser Arbeit war es, die analgetische Wirksamkeit der Akupunktur bei Tumorschmerzen sowie den Einfluss der Akupunkturdosis auf die Schmerzreduktion zu untersuchen.
Material und Methoden: Die Datenbanken Medline (Ovid), EMBASE (Ovid) und Cochrane Central Register of Controlled Trials (Ovid) wurden nach randomisierten kontrollierten Studien (RCTs) durchsucht, die manuelle (MA), elektrische (EA) und/oder aurikuläre (AA) Akupunktur zur Behandlung von Tumorschmerzen untersuchen. Die Ergebnisse dieser Studien wurden in einer Metaanalyse und Subanalyse für die Akupunkturmodalitäten ausgewertet. Primärer Outcome war die Veränderung der Schmerzintensität, gemessen als mittlere Differenz (MD) auf der numerischen Rating-Skala (NRS). Mithilfe von Meta-Regressionen wurde die Beziehung zwischen Dosierung und Schmerzreduktion ermittelt.
Ergebnisse: 14 RCTs mit 790 Patient_innen wurden in die Metaanalyse eingeschlossen. Die gepoolte Effektgröße zeigte eine signifikante Schmerzreduktion von -1,50 Punkten ([95% CI: von -2,41 bis -0,60], p<0,01). In der Subanalyse zeigte AA den stärksten analgetischen Effekt (MD: -3,02 [95% CI: von -17,48 bis 11,43]). Die Meta-Regression zeigte, dass eine höhere Anzahl an Sitzungen (beta: -0,06 [95% CI: -0,12 bis 0,00], p=0,05), Wochen (beta: -0,16 [95% CI: -0,31 bis -0,02], p=0,03) und eine höhere Intensität (beta: -0,40 [95% CI: -0,76 bis 0,04], p=0,03) mit einer stärkeren Schmerzreduktion assoziiert waren.
Diskussion: Die Ergebnisse der Analyse deuten darauf hin, dass Akupunktur, insbesondere AA, bei der Behandlung von Tumorschmerzen wirksam ist und dass die Dosierung eine Rolle für das Ausmaß der Schmerzreduktion spielen könnte. Weitere standardisierte Studien sind erforderlich, die mit methodischer Strenge,

präzisen Protokollen und unter Berücksichtigung der Dosis durchgeführt werden, um auch eine Implementierung in die klinische Praxis zu erzielen.

Abstract

Introduction: Current guidelines recommend acupuncture as an integrative treatment approach for cancer pain. The efficacy and mechanism of action of acupuncture are increasingly being studied according to Western scientific standards. Dosage is a factor that has not been sufficiently investigated but is important for the accuracy of research results and for socio-economic aspects in the implementation of the multimodal therapy concept. The aim of this thesis was to investigate the analgesic efficacy of acupuncture for cancer pain and the influence of acupuncture dose on pain reduction.

Materials and Methods: The databases Medline (Ovid), EMBASE (Ovid), and Cochrane Central Register of Controlled Trials (Ovid) were searched for randomized controlled trials (RCTs) using manual (MA), electrical (EA), and/or auricular (AA) acupuncture for the treatment of cancer pain. The results of these studies were assessed in a meta-analysis and sub-analysis of acupuncture modalities. The primary outcome was the change in pain intensity, measured as the mean difference (MD) on the numerical rating scale (NRS). Meta-regressions were used to determine the relationship between dosage and pain reduction.

Results: 14 RCTs with a total of 790 patients were included in the meta-analysis. The pooled effect size showed a significant pain reduction of -1.50 points ([95% CI: -2.41 to -0.60], $p<0.01$). In the subanalysis, AA demonstrated the strongest analgesic effect (MD: -3.02 [95% CI: -17.48 to 11.43]). Meta-regression showed that a higher number of sessions (beta: -0.06 [95% CI: -0.12 to 0.00], p=0.05), weeks (beta: -0.16 [95% CI: -0.31 to -0.02], p=0.03) and intensity (beta: -0.40 [95% CI: -0.76 to 0.04], p=0.03) were associated with greater pain reduction.

Discussion: The results of the analysis suggest that acupuncture, and in specific AA, is effective in the treatment of cancer pain and that dosage may play a role in the magnitude of pain reduction. Further high-quality studies conducted with

methodological consistency, precise protocols, and a focus on dosage are needed in order to enable successful implementation in clinical practice.

Abbreviations and their Explanations

AA: auricular acupuncture

ABVN: auricular branches of the vagus nerve

ACC: anterior cingulate cortex

ACh: acetylcholine

ACTH: adrenocorticotropic hormone

ALT: anterolateral tract

AMYG: amygdala

ANS: autonomic nervous system

AR: arcuate nucleus

ATP: adenosine triphosphate

BPI-SF: brief pain inventory short form

CBT: cognitive behavioral therapy

CCK-8: cholecystokinin octapeptide

CI: confidence interval

CMP: Conditioned Pain Modulation

COX-2: cyclooxygenase-2

CT: chemotherapy

CGRP: calcitonin gene-related peptide

CONSORT: Consolidated Standards of Reporting Trials

df: degrees of freedom

DLT: dorsolateral tract

DNIC: diffuse noxious inhibitory control

EA: electroacupuncture

EORTC-QLQ-C30: EORTC core Quality of Life Questionnaire

Ep: epinephrine

FDA: Food and Drug Administration

fMRI: functional magnetic resonance imaging

GABA: γ-aminobutyric acid

HAMD: Hamilton Depression Rating Scale

HPA: hypothalamus-pituitary-adrenal

HT: hormone therapy

IASP: International Association for the Study of Pain

IL: interleukin

LC: locus coeruleus

LSA: lateral septal area

LTD: long-term depression

LTP: long term potentiation

MA: manual acupuncture

MCID: minimum clinically important difference

MD: Mean Difference

MDD: major depressive disorder

N(A/C): Number of Patients in Acupuncture Group / in Control Group

NAcc: accumbens nucleus

NC: caudate nucleus

NE: norepinephrine

NR(M): nucleus raphe (magnus)

NRS: numeric rating scale

NSAID(s): non-steroidal anti-inflammatory drug(s)

NTS: nucleus of the solitary tract

PAG: periaqueductal gray

PET: positron emission tomography

PG(E): prostaglandin (E)

PO: preoptic area of the hypothalamus

PVH: paraventricular nucleus of the hypothalamus

QoL: quality of life

RCT(s): randomized controlled trial(s)

RR: risk ratio

RT: radiation therapy

SA: sham acupuncture

SD: standard deviation

SMD: standardized mean difference

SP: substance P

Sp: septal area

SPMs: specialized proresolutive mediators

SNRI: selective norepinephrine reuptake inhibitors

STRICTA: STandards for Reporting Interventions in Clinical Trials of Acupuncture

SSRI: selective serotonin reuptake inhibitors

STT: spinothalamic tract

TCA: tricyclic antidepressants

TENS: transcutaneous electrical nerve stimulation

TCM: Traditional Chinese Medicine

TNFα: Tumor Necrosis Factor α

UC: usual care

VAS: visual analog scale

WDR: wide dynamic range

WMD: weighted mean difference

WHO: World Health Organization

5-HT: 5-hydroxytryptamine = serotonin

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1. Introduction

1.1. Background on Cancer and Pain Management

1.1.1. Cancer – a Global Burden

Cancer is a major contributor to global mortality and a major challenge to improving life expectancy in all countries. The World Health Organization (WHO) estimates that there were 20 million new cases of cancer in 2022. Further estimates suggest that one in five individuals will develop cancer over the course of their lifetime, with a rate of one in nine among men and one in twelve among women. (1) Further analysis predicting future trends indicates a 77% increase from the 20 million new cases estimated for 2022, resulting in more than 35 million new cancer cases by 2050. These projections demonstrate that cancer is not only a significant current burden on the healthcare system, but also a substantial future challenge. In 2019, the WHO published estimates that 9.7 million deaths were attributable to the disease. (1) Cancer was identified as the primary or secondary cause of death before the age of 70 in 112 of the 183 countries surveyed, and as the third or fourth leading cause in a further 23 countries. In general, the incidence and mortality rates associated with cancer are increasing at a rapid pace on a global scale. This reflects both the aging of the population and population growth, as well as changes in the prevalence and distribution of the main risk factors for cancer, several of which are associated with socioeconomic development. (1)

1.1.2. Pain in Cancer Patients

Pain is one of the most feared and distressing symptoms in cancer patients. (2) In order to provide a more accurate context, it is essential to understand the definition of cancer pain as outlined by the International Association for the Study of Pain (IASP) Task Force for the Classification of Chronic Pain: "Causes of cancer-related pain include the tumor itself or its metastases inflaming or eroding bone, viscera, or nerves, or pain related to tissue or nerve damage induced by cancer treatments (surgery, chemotherapy (CT), and radiation therapy (RT),

hormone therapy (HT) and similar)” (3). This definition encompasses a number of potential causes and triggers of pain in cancer patients, which will be discussed in more detail in another section. Two-thirds of patients experience pain as a direct result of the primary tumor, while one-third develop pain as a consequence of therapy or indirect effects of the disease, such as osteoporosis, immobility, or infections. (4) Despite advances in treatment modalities and a more measured approach to opioid therapy, the prevalence of cancer pain has remained unchanged, with approximately one-third of cancer patients experiencing inadequate treatment. (5) However, effective symptom control and pain management are critical to patient survival and quality of life (QoL). (6)

1.1.3. Cancer Pain Management

A variety of factors contribute to the prevalence and impact of cancer pain in today´s population. The combination of an aging population, new treatment options that improve survival in cancer patients, and the presence of multiple comorbidities in cancer patients has led to an increase in not only the prevalence but also the complexity of pain and other symptoms associated with cancer. (5) The heterogeneous nature of pain etiology requires a precise definition of pain to improve the assessment and management of cancer pain. As a preliminary step, it is helpful to recall the physiological and pathophysiological processes associated with pain.

1.1.3.1. Pain Physiology

In addition to its temporal course, pain can be categorized according to its physiology. A distinction is made between nociceptive, neuropathic and mixed pain. (5) Nociceptive pain is further subdivided into somatic and visceral pain. Somatic pain occurs in superficial structures, such as the skin, musculoskeletal and articular systems. Visceral pain occurs in organs located in body cavities, such as the thorax or abdomen. (7) Nociceptive pain is caused by stimulation of the nociceptors. This can be caused by mechanical, thermal, or chemical stimuli, or a combination of these, which is referred to as polymodal. The noxious stimuli

are then converted into electrical signals in a process known as transduction. These are then transmitted by afferent nerve fibers to the dorsal horn of the spinal cord, the brainstem, and onward through connections, which include the thalamus, primary and secondary somatosensory cortices, and anterior cingulate cortex (ACC). As central structures, the prefrontal cortices, and the amygdala (AMYG) play a particularly important role in the modulation of pain. Thus, perception takes place in the brain, where pain is interpreted in terms of its location and intensity, emotional and behavioral processing, and comparison with previous pain experiences and learned behaviors. (5,8) The transmission of pain stimuli from the peripheral nervous system (PNS) to the central nervous system (CNS) and also vice versa can be influenced by synaptic inhibitory and excitatory messenger substances. These include neurotransmitters (such as glutamate and γ-aminobutyric acid (GABA)), gasotransmitters, monoamines (including dopamine, epinephrine (Ep), norepinephrine (NE), 5-hydroxytryptamine, better known as serotonin (5-HT) and histamine), as well as peptides (such as substance P (SP) or opioid peptides), and purines (such as adenosine triphosphate (ATP) and adenosine) and acetylcholine (Ach). (8) These will be relevant again in the sections discussing the analgesic mechanisms of action of acupuncture. Neuropathic pain, on the other hand, usually results from damage to nerves or from repeated pain sensitization of the PNS or CNS. Inflammatory mediators such as bradykinin, cytokines, prostaglandins (PGs) and 5-HT may also play a role here. These mediators are released when peripheral tissue is damaged, where they cause direct stimulation of the nociceptors. As a result, the activation threshold for afferent pain transmission is lowered. (8) Aδ fibers are responsible for the transmission of fast, sharp pain, while C fibers are responsible for slower, dull pain. Aβ fibers are responsible for transmitting sensations of touch, pressure, and vibration, which are not typically associated with pain. (5)

1.1.3.2. Pathophysiology of Cancer-Related Pain

Based on the understanding of pain physiology, tumor pain can now be studied in more detail. The etiology of pain in tumor patients is complex and multifactorial,

with a multitude of potential causes and processes that can be attributed to cellular, tissue, and systemic changes. These processes are caused by the proliferation, invasion, and migration of cancer cells. (7) The occurrence of pain is then attributed to interactions between cancer cells, the PNS and CNS, and the immune system. It is important to distinguish between pain experienced by cancer patients and pain directly caused by the tumor itself. The etiology of pain in cancer patients can be complex, and in some cases, it may not be possible to identify the precise origin of the pain. However, identifying the source as accurately as possible is essential for a more precise and effective treatment plan. (7) The underlying cause of pain in tumor patients can be classified into the following categories:

- Presence and/or growth of tumor and/or metastases
- Consequences of anticancer therapies, including diagnostic procedures, surgery, RT, CT, HT, immunotherapy, and molecular therapy.
- Processes indirectly related to the tumor or treatment, such as infections and metabolic disorders.
- Processes that are not related to the cancer or treatment, but may still occur in tumor patients. (7)

From a physiological standpoint, tumor pain can be classified as either nociceptive pain, neuropathic pain, or a combination of both. (7)

- Nociceptive tumor pain: usually caused by irritation or decreased stimulation threshold of nociceptors, tissue infiltration by the tumor, or metastases.
- Neuropathic tumor pain: results from injury to the PNS or CNS. It is dull in character, difficult for patients to tolerate, and more complicated in terms of therapeutic response.
- Mixed pain: tumor pain very often shows components of both causes and characteristics of pain, mixed with the effects of inflammatory processes, ischemic processes, and processes running in parallel at multiple sites. (7)

1.1.4. Treatment of Cancer Pain

In a new edition of the guidelines published in 2019, the WHO specified the treatment of cancer pain. The goal of cancer pain management was redefined as "to reduce pain to a level that allows an acceptable quality of life" (9). The WHO guidelines specify the treatment of cancer pain and exclude treatment recommendations for pain in cancer patients caused indirectly or unrelated to cancer therapies. (9) Therefore they use the same definition of cancer pain that is used in this thesis. Although the WHO guidelines emphasize the need for a multidisciplinary approach to the management of cancer pain, they focus primarily on pharmacologic recommendations. In order to apply such a comprehensive approach to the patient and to develop an optimal therapy according to the principle "for the individual", it is therefore important to understand the basics of pharmacological therapies (9).

1.1.4.1. Pharmacological Treatment

In accordance with the WHO and other internationally recognized guidelines, pharmacologic treatment options for cancer pain include the use of non-steroidal anti-inflammatory drugs (NSAIDs) and/or opioids, as well as the incorporation of adjuvant drugs such as steroids, antidepressants, and anticonvulsants. (6,9–11) Another chapter of the WHO guidelines addresses the treatment of bone pain in tumor patients with bisphosphonates, monoclonal antibodies, and RT. However, the main focus of the treatment principles is on the use of opioids. (9)
The WHO 3-step analgesic ladder, first introduced in 1986, continues to serve as the foundation for the treatment of cancer pain (12):

- Step 1: NSAIDs or acetaminophen +/- adjuvant
- Step 2: Opioid for mild to moderate pain, such as codeine
    - + non-opioid
    - + adjuvant
- Step 3: Opioid for moderate to severe pain, such as morphine, oxycodone, fentanyl
    - + non-opioid

- + adjuvant (9)

The WHO emphasizes that this sequential approach is merely a basic concept, intended primarily for educational purposes. It is intended only as a framework for managing cancer pain and does not replace the need for individualized treatment decisions for each patient. (9)

1.1.4.1.1. Non-Opioids

Non-opioid alternatives should be prioritized at the beginning of pain management whenever possible. For patients with more severe pain, a combination of non-opioid and opioid medications should be considered to keep opioid doses as low as possible and reduce their adverse effects. (9,13)

1.1.1.1.1.1 Acetaminophen

Acetaminophen, also known as Paracetamol, has an antipyretic and analgesic effect, but no anti-inflammatory properties. (6) Because of its hepatotoxic effects, its use is only recommended after a thorough risk-benefit assessment. (13) There is no evidence to suggest that it is effective for tumor pain. (10)

1.1.1.1.1.2 NSAIDs

NSAIDs produce an analgesic effect by inhibiting biosynthesis of PGs. PGE plays an important role as inflammatory mediator in both the development and maintenance of pain. (6) Several factors must be considered when using NSAIDs. In particular, long-term use may lead to bleeding of upper or lower gastrointestinal tract. In addition the nephrotoxic effects should be considered, which also lead to complications, especially when combined with other nephrotoxic drugs, such as chemotherapeutic agents, and impaired kidney function. (6) Furthermore, the use of NSAIDs has been shown to be associated with an increased risk of cardiovascular complications. The risk of adverse effects from NSAIDs increases with advancing age. (6) Given the aging population, this problem therefore affects a large group of patients.

1.1.4.1.2. Adjuvants

Adjuvant analgesics for the treatment of tumor-related pain include anticonvulsants, such as pregabalin or gabapentin, antidepressants, including selective serotonin and norepinephrine reuptake inhibitors (SSRIs and SNRIs) and tricyclic antidepressants (TCA), corticosteroids, and local anesthetics, such as lidocaine patches. (6) The use of these agents is intended to enhance the efficacy of opioids, reduce their dosage, and minimize adverse effects. In addition, the use of adjuvant analgesics may also be beneficial in patients who do not respond well to opioids, particularly in cases of neuropathic pain. (6) For purposes of completeness, cannabinoids and medical cannabis are also mentioned, as there are currently three substances approved by the Food and Drug Administration (FDA): dronabinol, nabilone, and cannabidiol. The efficacy of cannabinoids has only been the subject of a limited number of studies, and the available data is contradictory. In addition, the safety profile of these agents remains unclear. In contrast, medical marijuana is not approved by the FDA, although its widespread use among cancer patients has been documented. (6)

1.1.4.1.3. Opioids

For more than two centuries, the opioids have been the most important treatment for severe pain, including cancer pain. For the treatment of moderate to severe cancer pain opioids are recommended in adequate doses and in combination with non-opioid analgesics and adjunctive therapies. (6,9) The primary mechanism of action of opioids is to bind to μ-opioid receptors in the nociceptive transduction pathway, thereby inhibiting depolarization of afferent nociceptive neurons and thus producing analgesia. Over time, various subtypes of μ-opioid receptors have been identified, explaining the differences in binding and effects of μ-opioid agonists and a divergent spectrum of side effects. (6) It should be noted, however, that there is still considerable interindividual variability in response to these drugs. (14) The most used opioid analgesics for the treatment of cancer pain are pure agonists, including morphine, oxycodone, oxymorphone, and fentanyl. Short-acting agonists, such as morphine, hydromorphone, fentanyl, and oxycodone, are preferred over long-acting agonists, such as methadone and levorphene, due to

their better titratability. (6) The WHO has identified tramadol, fentanyl, and methadone as essential drugs for the management of cancer pain. (15) In all guidelines gradual titration of the chosen opioid is a central principle, with the aim of maintaining better control over analgesic and also adverse effects. (6,9,13) It is not unusual for patients to experience adverse effects associated with opioid use. The most reported symptoms are constipation and nausea. Other common side effects include sedation, pruritus, urinary retention disorders, and endocrine changes affecting the hypothalamic-pituitary-gonadal axis. (6,11,14) Although rare, the development of respiratory depression is possible and can be life-threatening. This may be caused by overdose or accumulation of the administered drugs and their metabolites due to hepatic or renal impairment or pharmacokinetic and pharmacodynamic interactions with other substances. Another serious adverse effect is neurotoxicity, which can contribute to the severe clinical picture of delirium, with patients at the end of life being particularly at risk. (14)

1.1.4.2. Non-Pharmacological Treatment

As mentioned above, pharmacological treatment is associated with a multitude of adverse effects and may lead to complications and further problems, especially in elderly and chronically ill patients. With this in mind recently proposed guidelines advocate for the incorporation of non-pharmacological integrative therapeutic modalities that can augment and improve the efficacy of pharmacological interventions. (10,13) The WHO refers to this aspect of treatment as the integrative component of comprehensive cancer pain management. (9) Recent oncology guidelines list a variety of interventional procedures, including intrathecal drug administration, nerve blocks, neuromodulation strategies, palliative RT, and other procedures. The aim is to reduce the need for opioids in patients experiencing adverse effects or to prevent their occurrence. (6,10,11,13) In a paper published in 2023, Anekar et al. extended the WHO 3-step ladder to include these interventional and minimally invasive procedures, declaring them the fourth step in the established system. (12) However they represent an intensification of pain therapy. But there are also recommendations for the inclusion of non-

pharmacological procedures, which are regarded as a general extension of therapy. Following the picture of the WHO ladder, these could be considered as level zero, the basic level. The guidelines recommend measures that address the physical, social, psychological, and spiritual dimensions of the patient. (6,9,13) These include cognitive modalities, such as cognitive behavioral therapy (CBT), active coping training, or psychiatric care, but also nutritional modalities, social work, and physical modalities, such as physiotherapy and the application of acupuncture. (13)

1.2. Acupuncture in Cancer Pain

The previous sections explain pain and its mechanisms from the perspective of current research in Western medicine. In acupuncture, however, pain is viewed according to the concepts of TCM (with the exception of trigger point acupuncture). In TCM pain is considered a clinical manifestation of a Qi imbalance. (8) Qi is a fundamental substance often translated as "energy" and is essential to the vitality and function of the organism. (16) For this reason, even when there is only a single point of pain, the clinical examination in TCM is very detailed. It includes palpation of various pulses, examination of the tongue, and a close examination of physical characteristics. A detailed history is taken, including a thorough analysis of the pain, sleep, bowel movements, exercise tolerance and emotions. This is essential in diagnosing the deficiency or stagnation of Qi that is causing pain. (8) This is particularly relevant to the practice of acupuncture. However, the lack of understanding of the mechanisms of acupuncture from a Western perspective, along with the absence of correlating anatomical structures, are factors that may have contributed to the incomplete acceptance of acupuncture in our culture. (17) Nevertheless, the increased interest in acupuncture has led to significant advances in research in this area. This thesis reviews the mechanisms of action of acupuncture according to Western research standards and knowledge. This is essential to fill gaps in our knowledge and to reduce skepticism about the empirical medicine of TCM. It should be noted here, however, that the exact mechanism of action of acupuncture is currently not fully

understood. Given this fact and the numerous mechanisms that have been discussed as contributing to the efficacy of acupuncture, this thesis does not have the scope to address all these mechanisms. It is evident that the effects of acupuncture points vary depending on the networking and activation of specific circuits in the nervous system. However, the acupuncture points used for pain relief are not necessarily the same as those used for other conditions, such as cardiovascular disorders. (17,18) Therefore, this section focuses on outlining the potential mechanisms of pain inhibition and modulation in acupuncture that have been researched. This is followed by a section reviewing the current research that has examined the efficacy of acupuncture in treating cancer pain. As the focus of this thesis is on dosage, the importance and relevance of acupuncture dosage is then discussed.

1.2.1. The Pain-Inhibiting and Pain-Modulating Mechanisms of Acupuncture

Acupuncture points can be found in a variety of locations, including muscles and tendons, joints, bony furrows, and the suture lines of the skull. (21) Over time, many theories have been proposed to explain what exactly acupuncture points are, but they have not been supported by sufficient proof. However, improved technology has allowed neurobiological research to progress, providing new insights. It should be noted that despite the following substantial findings, there are still some inconsistencies and conflicts that the teaching of the TCM system of acupuncture points, the “meridian system”, brings from a neuroanatomical point of view. (19) Nevertheless, the results of in-depth research show the close relationship between acupuncture points and peripheral nerves, and it has been clearly demonstrated that the PNS forms the basis of acupuncture points and meridians, while the CNS is responsible for signal processing. It has also been found that the nerves at the acupuncture points are often part of the same spinal cord segment as those of the corresponding organs, or at least within reach of them. (19) There are also interesting differences in the nerves distributed at acupuncture points. They differ in their distribution density, the thickness of their

fibers and also the shape of their endings. This results in differences in the technique and depth of needling required at each acupuncture point, and in the fact that the De Qi sensation, which will be discussed in more detail in the next section, varies from acupuncture point to acupuncture point. (19) The pain-modulating and pain-inhibiting effects of acupuncture result from the interaction of various mechanisms at different levels. (20,21) Stimulation of acupuncture needles by manual application or weak current is thought to create a neurophysiological basis that can alter the activity of both PNS and CNS pathways. (17) But there are local, segmental, spinal, cerebral, and systemic mechanisms involved that contribute to the therapeutic effect. (20,21) The following section discusses some of the mechanisms that have been the subject of intense research over the past several decades.

1.2.1.1. Periphere Mechanisms

An important discovery was that acupuncture is only effective in relieving pain when the aforementioned De Qi sensation occurs during needle manipulation. This is often perceived by patients as a feeling of numbness, heaviness or fullness, sometimes also as soreness, tingling or radiating. (8,17,19) At the same time, the acupuncturist may also feel De Qi, which is considered in acupuncture to be the "arrival of Qi". In this case, the acupuncturist perceives a sensation in the fingers inserting the needle that can be described as a pulling sensation and increased resistance to further movement, comparable to a fisherman's perception of a biting fish. (8,22) Studies have shown that the application of the local anesthetic procaine to acupuncture points leads to a loss of perception of the De Qi sensation and thus of the pain-relieving effect of acupuncture. This indicates that the De Qi sensation is essential for pain relief and can therefore also be used by the acupuncturist to check the correct needle position. (17,22) However, the mechanism by which De Qi occurs is not yet clear. But there are research approaches that suggest its origin in muscle contractions and studies that suggest its origin in connective tissue. In any case, the research on De Qi is a promising approach to understanding the pain-relieving effects of acupuncture. One

approach is that the described sensation may be caused by muscle impulses induced by acupuncture. (8,22) A study showed that there is a positive correlation between the intensity of the De Qi feeling in both the patient and the acupuncturist and the magnitude of the electromyography induced by the individual acupuncture points. (23) Presumably polymodal receptors, especially in the muscles, play an important role here, but the possibility that it originates in other deeper tissues cannot be ruled out. (22) Another possible origin, recently suggested by Langevin et al., is the connective tissue. The basis for this is the mechanical coupling between the needle and the connective tissue, which holds the needle in the tissue. It results from the tissue wrapping around the needle as it is rotated. The wrapping may trigger and transmit a mechanical signal to the tissue. (8,22,24,25) There is also some evidence that mast cells localized in the connective tissue may play a role. (8,22) Another specialty of analgesic acupuncture is the acupuncture of myofascial trigger points, known as dry needling. Although these trigger points do not generally correlate with the classical acupuncture points, they can also be used in the traditional setting as “Ashi points”, defined as local pressure dolent points. The acupuncture needle is inserted into a hardened muscle cord (taut band), causing muscle twitches, referred to as a “twitch response”, which produces a detonating and analgesic effect by stimulating the motor endplate. (20) For acupuncture points evolving from the classical teachings of TCM, it has been determined that, among other mechanisms, type II and III afferent nerve fibers, including C, Aβ and Aδ fibers, are responsible for the analgesic effect. (20–22) This mechanism leads to a connection to the nervous system, linking the local action to spinal and central mechanisms, which will be discussed in more detail in the next section. Locally, stimulation of C and/ or Aδ fibers, presumably mediated by an axon reflex, leads to the release of various neuropeptides such as calcitonin gene-related peptide (CGRP) and SP. This leads to increased blood flow in the surrounding area and possibly also in the deeper layers. CGRP also has an anti-inflammatory effect at low doses as in acupuncture. (20,21,26,27) A key role in the mode of action of acupuncture is the release of ATP from skin cells initiated by the needle stimulus, which is also significantly involved in the analgesic effect of

acupuncture. (27) Other mediators released locally by the tissue damage caused by the needle include bradykinin, histamine and 5-HT. (22) The mild injury, such as the prick of an acupuncture needle, may also activate the peripheral cannabinoid CB2 receptors on keratinocytes, followed by a peripheral release of β-endorphins, which is thought to contribute to the analgesic effect. (21) The involvement of the opioid system is not only at the peripheral level, where it has anti-inflammatory and analgesic effects, but also at the central level, which represents an interweaving of effects in the nervous system and will therefore be discussed in a separate section with other messenger substances. (20)

1.2.1.2. Segmental and Spinal Mechanisms

The analgesic effect of acupuncture via the spinal cord can be achieved by inhibiting nociceptive impulses. There is an effect that follows the principles of segmental innervation using dermatomes, myotomes, viscerotomes, and sclerotomes, which share the same innervation and sensory input entry into the dorsal horn of the spinal cord. (22) As previously stated many traditional acupuncture points lie within or within reach of the same segment as the structure targeted for the effect. (19) Examining the segmental mechanisms in acupuncture analgesia, these mechanisms might explain why needling acupoints in the region of pain, such as “Ashi points”, has the best analgesic effect. (28) Both presynaptic and postsynaptic inhibition play a role, with the activated mechanism depending on the acupuncture modality and the intensity of the stimulus. (20,22) Stimuli with a slightly painful intensity activate Aδ fibers. This leads to a long-lasting inhibition of the transmission of nociceptive impulses to the neurons of the dorsal horn of the spinal cord. This effect lasts much longer than the duration of the stimulation and is referred to as "long-term depression" (LTD). The underlying mechanism is probably an altered plasticity of the dorsal horn with reduced synaptic transmission strength. This is particularly successful in the treatment of chronic pain with the formation of a pain memory, which is based precisely on increased synaptic impulse transmission strength. (20) In contrast, non-painful stimuli activate Aβ

fibers. The mechanism by which analgesia is mediated through the spinal cord was first proposed in 1956 by Melzack et al. as the gate control theory (29). This theory was based on the premise that pain is not exclusively activated by noxious stimuli at the tissue level, but that modulation of pain signals in the spinal cord plays a critical role. (29) This theory could not be fully proven in experiments and was later updated by Melzack himself to the “neuromatrix theory” (30). Due to the clarity of the original model, it will be used here to illustrate the mechanism. It is evident that, as previously stated, pain stimuli transmitted via C and Aδ fibers trigger the activation of higher processing centers in the brain. However, when Aβ fibers are activated by touch, friction, or vibration, rather than by pain, they can close a so-called “gate” in the substantia gelatinosa. The substantia gelatinosa is an area of the dorsal horn of the spinal cord that acts as a filter station, inhibiting and attenuating pain signals when activated. (27,29) Activation of Aβ fibers therefore results in a segmental inhibition of nociceptive inputs via the neurotransmitter GABA. However, this mechanism has only a short-term effect and is therefore not the only explanation for the pain-relieving potential of acupuncture. (29) A further contribution to the modulation of pain is made by the propriospinal antinociceptive neurons, which exert a bilateral effect by means of a heterosegmental action. (20,21) Another important mechanism that might explain the effects of acupuncture on organs is the somatovisceral reflex arc. Afferents from the skin and internal organs converge on the same population of nociceptive neurons in the spinal cord. This explains the phenomenon of misdirected nociceptive visceral input to the body surface, known as "head zones". However, this effect, caused by the somatovisceral reflex arc, probably also works in reverse, leading to altered regulation in the viscera by cutaneous nociceptive stimuli from acupuncture. (20) Another mechanism that may contribute, especially in the long term, is the segmental reflex response of the autonomic nervous system (ANS) by improving tissue perfusion. (20,27)

1.2.1.3. Central and Systemic Mechanisms

In addition to effects of spinal interneurons, there are supraspinal mechanisms that determine the analgesic effect of acupuncture. Similar to the “gate control theory”, the mechanism of "diffuse noxious inhibitory control" (DNIC) is based on the principle of "pain inhibits pain". In the case of DNIC, however, the inhibition applies to all areas of the body without restriction to segments. In the literature, DNIC is often equated with the concept of Conditioned Pain Modulation (CMP), with DNIC being primarily the neurophysiological mechanism and CMP being primarily the behavioral correlate. (8,20,31) However, DNIC can only be triggered by the activity of Aδ or Aδ and C peripheral fibers and is maintained by a complex loop involving supraspinal structures. In this context, Bars et al. were able to show the involvement of neurons of the subnucleus reticularis dorsalis in spinobulbo-spinal loops that send descending projections through the dorsolateral funiculus, ending in so-called wide dynamic range (WDR) neurons at all levels of the dorsal horn of the spinal cord. (32) In the dorsal horn, there are at least two types of secondary spinal neurons involved in pain modulation: the nociceptive-specific neurons and the WDR neurons, which are involved in the "wind-up" of chronic pain. The pain modulating effect is the result of the inhibition of WDR neurons by the DNIC, whereby the acupuncture stimulus could function as an activating pain stimulus in this context. However, the studies conducted to date on this topic are limited, and the short-acting effect of DNIC is at odds with the effect of acupuncture. Nevertheless, it is considered a promising approach to focus further research on investigating acupuncture as a modulator of the DNIC. (8,20,31) An important pillar of acupuncture analgesia is the activation of descending inhibition, the body's own pain defense. Clinical and experimental studies have shown that there is an interplay between the signaling pathway of the acupuncture stimulus and the pain pathways. (22) The main pain pathways have been researched in detail and the two most important ascending pain pathways are the spinoparabrachial tract and the spinothalamic tract (STT). (33) Experiments have shown that acupuncture signals ascend via the ventrolateral fascicle of the spinal cord. There they activate a supraspinal structure located mainly in the medial reticular formation of the brainstem. Via the dorsolateral fascicles, the axons then reach the segmental

spinal cord level, where they inhibit signal transduction of ascending nociceptive afferent signals in the substantia gelatinosa of the dorsal horn by enhancing descending inhibitory impulses. (20,28) Numerous experiments have shown that in addition to the spinal cord, the reticular formation, the nucleus raphe magnus (NRM), dorsal raphe nucleus, locus coeruleus (LC), periaqueductal gray (PAG), arcuate nucleus (AR), preoptic area (PO) of the hypothalamus, thalamus, caudate nucleus (NC), septal area (Sp), accumbens nucleus (NAcc), putamen, AMYG, hippocampus and cortex play a role, although some relevant regions are certainly still unknown. (20,28) Studies of brain lesions further revealed that the source of descending inhibition is predominantly attributed to the NRM and its adjacent structures. (34) Descending inhibition is mediated by modulators, such as opioid peptides, transmitters (5-HT, ACh, etc.) and other messengers. (28) Bruce Pomeranz was one of the fundamental researchers on the analgesic mechanisms of acupuncture. His early theory was published as the "endorphin hypothesis". Although some of its components have never been fully proven, the fundamentals of the theory are obvious, and the clarity of his model again is useful in illustrating the connection between the body's anti-nociceptive system and opioids as messengers. The acupuncture needle stimulates nerve fibers, which then transmit the stimulus down the spinal cord to three different centers. These are the medulla oblongata, the midbrain, and the hypothalamic-pituitary complex. These three levels then contribute to the analgesic effect via interactions resulting in the inhibition of signal transmission of pain. (35) Figure 1 illustrates this schematic cycle in detail.

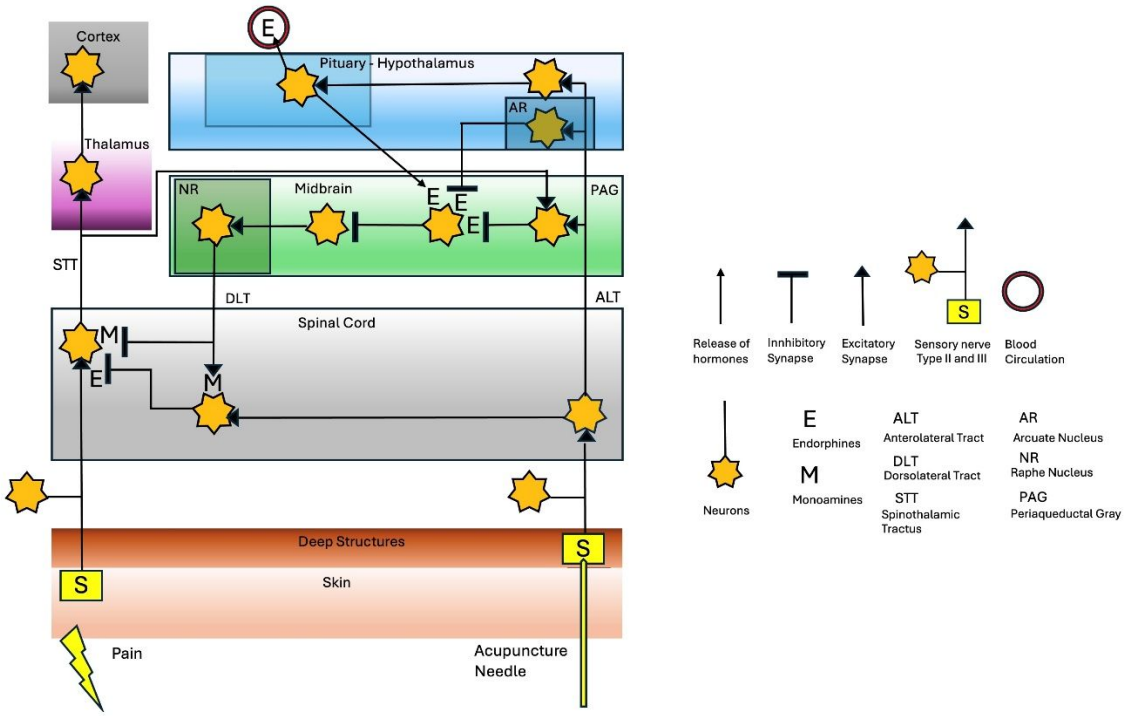

Figure 1: Transmission of Pain Stimulus. A pain stimulus activates sensory nerves that excite neurons in the spinal cord. These in turn activate the thalamus via the spinothalamic tract (STT). The stimulus is then transmitted to the cortex. The acupuncture needle activates type I and II sensory nerves, which then release enkephalins and dynorphins (E), but not β-endorphins, at the spinal level. These endogenous opioid peptides (E) bind to opioid receptors and block sensory afferents. (18,36) In addition, the activated cell in the spinal cord projects via the anterolateral tract (ALT) to the midbrain, where it activates cells of the periaqueductal gray (PAG). These inhibit additional interneurons via enkephalins (E), which in turn activate the descending raphe system, the raphe nucleus (NR). This stimulates cells in the dorsolateral tract (DLT) of the spinal cord, causing the release of monoamines, including 5-HT and NE, which directly and indirectly inhibit the transmission of pain from the spinal cord to the thalamus. In addition, neurons in the spinal cord project to the hypothalamic-pituitary complex at the third level. In this region, they excite two different neural networks. First, they excite neurons in the arcuate nucleus (AR), which in turn inhibits the midbrain circuit via endorphins, thereby indirectly inhibiting pain transmission (via the DLT). Second, they stimulate neuronal structures of the pituitary gland, which release β-endorphins (E) into the bloodstream and across the blood-brain barrier into the cerebrospinal fluid. These are thought to also affect pain inhibition via the midbrain. Modified from Pomeranz et al. (1996) (18).

In addition to the three interacting levels, the pituitary gland is thought to release adrenocorticotropic hormone (ACTH), which is thought to have an anti-inflammatory effect via the release of cortisol. (18) Other transmitters such as GABA are also thought to be involved in high-frequency stimulation of acupuncture points. Through numerous experiments, Pomeranz was able to show that the release of endorphins through acupuncture plays a significant role in pain inhibition. (35,37) For example, Pomeranz et al. showed in mice and cats that the

analgesic effect of acupuncture could be reversed by the administration of naloxone, supporting the involvement of endogenous opioids. (38) Another finding was that the analgesic effect of acupuncture could be transferred from one animal to another through the transfer of cerebrospinal fluid. (39) Later, the theory was extended to include the effects of electroacupuncture (EA), and it was shown that different opioid subtypes are released by different modalities. Lower EA frequencies (2 Hz) resulted in the release of enkephalin and β-endorphin, which bind to μ- and δ-opioid receptors, and higher frequencies (100 Hz) resulted in an increase in dynorphin, which binds to the κ-opioid receptor located in the dorsal horn of the spinal cord. (21,22,27,40,41) Recent research has further explored the role of opioids and has been able to demonstrate their importance in peripheral mechanisms through a modulatory effect on inflammatory pain. (22) The central role of opioids has been studied primarily in the context of different opioid receptors and opioid subtypes. (8) Furthermore, in connection with the study of the opioid system, it has been determined that an important structure in the endogenous opioid peptide system is the AR, which contains a high density of β-endorphin-containing neurons. Their axons extend to the lateral septal area (LSA), NAcc, PAG and LC. This may indicate that the AR plays a central role in mediating acupuncture analgesia. (22) In addition to opioid peptides, numerous other neurotransmitters and neuromodulators have been identified as contributing to the analgesic effect of acupuncture. (20,22,27) Due to the complexity of the respective relationships, some of these will be mentioned but not explained in detail. As mentioned above, Pomeranz was able to show in his early research that monoamines such as 5-HT participate in the antinociceptive effect. (37) 5-HT and its receptors are highly expressed in the CNS, especially in the NRM, which is important in the descending pain modulation system. Thus, ascending and descending serotonergic pathways emanating from this area are involved in pain modulation and acupuncture analgesia. (8,22) Furthermore, NE is involved via NE-containing neurons in the A1, A2, A4-7 nuclei of the brainstem, which are connected to the spinal cord via signaling pathways (forebrain, dorsolateral tract (DLT) of the spinal cord). Via noradrenergic projections from supraspinal nuclei

such as the lateral reticulare nucleus and LC to the dorsal horn, spinal α2-adrenergic receptors contribute to descending inhibition and pain modulation, particularly in neuropathic pain. (8,22) There are also studies that show the involvement of GABA, dopamine, glutamate, and others. (8,22) It is known that SP plays a crucial role in the signaling of peripheral and spinal nociception. Increased SP levels are found in patients with various pain conditions, inflammatory processes, stress and anxiety. (8) Acupuncture has been shown to decrease SP and increase β-endorphins in mice with cancer. (42) Opioids inhibit the release of SP. It is obvious that acupuncture inhibits the release of SP by activating the endogenous opioid system, thus supporting the pain modulating effect. (22) Furthermore, acupuncture has been shown to reduce cyclooxygenase-2 (COX-2) via the hypothalamus-pituitary-adrenal (HPA) axis. This reduction in COX-2, by interacting with the endocannabinoid system, stimulates an increase of opioids at the site of pain. It also results in lower levels of PGE-2, which further contributes to the analgesic effect. (43) Another bioactive substance has attracted particular attention in recent years and should therefore be mentioned here. Cholecystokinin octapeptide (CCK-8) is involved in many physiological processes. CCK-8 is the most potent antagonist of opioid activity and thus has an anti-analgesic effect. Thus, CCK-8 probably plays an important role in individual sensitivity to acupuncture via interpersonal differences in the release of CCK-8 and in the density of CCK-8 receptors that influence opioid activity. (22) In recent years, the study of the cerebral mechanisms of acupuncture using imaging techniques such as functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) has advanced and helped to complement the results of studies using various techniques such as stimulation and lesioning of brain nuclei and acupuncture-induced Fos expression. This has helped to identify numerous brain structures involved in the modulation of acupuncture analgesia. These include the rostral ventromedial medulla (mainly NRM), the PAG, the LC, the AR, PO, the centromedian nucleus, the thalamic nucleus submedius, the anterior pretectal nucleus, the habenular nucleus, the NAcc, the NC, the Sp, the AMYG, the ACC, and the paraventricular nucleus of the hypothalamus (PVH). (22) Acupuncture was

found to activate regions such as the PAG and NRM, which are associated with descending inhibitory pain modulation. (20,22) Furthermore, some studies show that several structures of the limbic system such as the insula, the ACC and others involved in pain perception are deactivated by acupuncture and thus contribute to analgesia. (8,20,22) An interesting approach made possible by these new imaging techniques is the investigation of the De Qi sensation, which, as already described, plays a decisive role in the effect of acupuncture. Hui et al. were able to correlate the negative activation of the cerebro-cerebellar and limbic systems with De Qi using fMRI on a group of patients. (44) The imaging technique was also used to show a difference between laser stimulation of an acupuncture point used for ophthalmologic diseases and a non-acupuncture point. While stimulation of the real acupuncture point elicited activity in visual brain regions, stimulation of non-acupuncture points did not. (45) Another study used fMRI images to show that brain activity is different at various times during acupuncture. During the needling phase, the AMYG and perigenual ACC showed increased activity and then dropped below normal levels. In contrast, the PAG and hypothalamus showed intermittent activity throughout the study period and even beyond the needling period. (46) A systematic review collected numerous studies that examined acupuncture using fMRI. It was found that the differences between real and sham acupuncture (SA) in brain response occurred in the middle cingulate cortex, and that the brain areas showing activity in response to acupuncture stimuli included a broad network of regions consistent with somatosensory, affective, and cognitive processes. (47) In addition, the ANS also plays a role in the effects of acupuncture, including analgesia, by influencing parasympathetic and sympathetic activity. The ANS can be activated by direct stimulation of the vagus nerve, which is particularly important for ear acupuncture and will be discussed in a separate section. However, it has been shown that stimulation of distal acupuncture points that are not directly on the vagus nerve can also lead to activation of the parasympathetic nervous system and thus indirectly produce analgesia. (8) Functional MRI studies have shown that supraspinal changes also occur after peripheral stimulation. Specific responses have also been observed in brain areas

associated with ANS regulation and pain. (8) The ANS-mediated anti-inflammatory reflex also seems to be an interesting approach, although a direct link to acupuncture analgesia has not yet been demonstrated. (48,49) It is also thought that acupuncture may inhibit the functional activity of the sympathetic nervous system. (28) Motivated to come full circle to the origin of acupuncture in TCM, a publication by Zhao et al. summarized the mechanism of action as the ability of acupuncture to modulate central homeostasis to produce analgesia, reflecting TCM's teaching that acupuncture is a mechanism that influences the balance between Yin and Yang. (22)

1.2.1.4. Analgesic Mechanisms of Auricular Acupuncture

The mechanism of action of auricular acupuncture (AA) can partly be explained by the sensory innervation of the ear by auricular branches of the vagus nerve (ABVN) and the associated influence on the ANS. (50) The discovery by Friedrich Arnold, Professor of Anatomy at the University of Heidelberg, who described a somatoparasympathetic reflex and made it known under his own name as the “Arnold reflex”, paved the way for this in 1832. He described stimulation in the area of the external auditory canal that led to a kind of cough reflex, as would be triggered by the vagus nerve. Other reflexes triggered by auricular stimulation, such as the gastroauricular phenomenon or the pulmonoauricular phenomenon, followed. (50) The afferent projections, in particular of the ABVN to the nucleus of the solitary tract (NTS) of the brain, presumably form the basis for the regulation of both the ANS and the CNS. The connections of the NTS to various visceral regions and many brain regions, such as the PVH, the central nucleus of the AMYG and other nuclei in the brainstem, can provide an explanation of how stimulation of the ABVN can regulate the ANS. (50,51) Another mechanism that could be triggered by ear acupuncture and contribute to the analgesic effect is the release of neurotransmitters such as catecholamines, β-endorphins, glutamate and 5-HT. (52) The latest research in the field of AA for the treatment of pain focuses primarily on the modulation of pain transmission via the cholinergic anti-

inflammatory signaling pathway and the HPA axis. This occurs particularly through the release of pro-inflammatory cytokines, such as interleukin (IL) 1β, IL-8, and Tumor Necrosis Factor α (TNFα), and specialized proresolutive mediators (SPMs). These substances contribute to anti-inflammatory processes, pain relief, pain sensation and support of tissue regeneration. (51,52) Further research has shown that AA can trigger the activation of the descending pain inhibitory signaling pathway previously described and thus contribute to pain relief. In addition, the gate control theory could also be transferred to AA. (52) These might be specific mechanisms contributing to the analgesic effect of AA.

1.2.2. Research and Evidence of Acupuncture in Cancer Pain

The efficacy of acupuncture in the treatment of pain has been investigated in a number of systematic studies. Some of them were conducted investigating acupuncture in the treatment of acute pain, showing its effectiveness. (53–55) A meta-analysis by Zhu et al. also showed an effective reduction in the score for abdominal pain with a weighted mean difference (WMD) of -1.45 [95% CI: -1.71 to -1.19; $p<0.0001$] in the treatment of acute pancreatitis, indicating effects for visceral pain. (56) For chronic pain, some meta-analyses have also produced results supporting the efficacy of acupuncture. (57–59) In addition, there are results of studies suggesting the efficacy of acupuncture for neuropathic pain. (60–62) Cancer pain has also been studied in numerous randomized controlled trials (RCTs). RCTs are considered the gold standard for evaluating the safety and efficacy of therapeutic interventions. There are several meta-analyses of RCTs that have investigated the efficacy and safety of acupuncture in the treatment of cancer pain. Some were not able to provide enough evidence for the treatments´ analgesic effect. (63,64) A systematic review and meta-analysis conducted by He et al. and published in the JAMA Oncology Journal demonstrated that acupuncture and/or acupressure was significantly associated with a reduction in cancer pain and a decreased reliance on pain medication. (65) A meta-analysis published by Chiu et al. in the European Journal of Cancer Care demonstrated that acupuncture is an effective method for relieving malignancy-related pain (effect size (*g*): -0.71,

[95%CI: -0.94 to -0.48]). (26) In 2024, Faria et al. published a systematic review and meta-analysis that similarly indicated that acupuncture is a potentially effective and safe approach for reducing cancer pain compared to no treatment (standardized mean difference (SMD): -0.90 [95%CI: -1.68 to -0.12], SA (SMD: -1.10 [95% CI: -1.59 to -0.61]) or usual care (UC) (SMD: -1.16 [95% CI: -1.38 to -0.93]). (66) Other systematic analyses have further supported the beneficial effects of acupuncture for cancer pain. (65,67) These meta-analyses help to determine the overall effect of acupuncture and its role in therapy. They also provide information about the quality of the studies and help improve further research by identifying the limitations.

1.2.3. The Importance of Dosage in Acupuncture for Cancer Pain

Research in recent decades has yielded promising results regarding the efficacy of acupuncture. However, one principal factor that determines the application of therapeutic concepts has long been neglected: dosage. The dose-response principle is primarily a domain of pharmacology. However, the question arises as to whether it also applies to acupuncture, since it has a decisive influence on the interpretation of study results, the conduct of studies and, above all, clinical implementation. (68) Few studies have examined the duration of acupuncture treatment. One study of fibromyalgia patients examined factors that may influence the effect of acupuncture and concluded that the frequency of treatment has a significant influence. Treatment three times a week resulted in significantly better pain relief than treatment once a week. (69) A well-known study by Ezzo et al. showed that in patients with knee osteoarthritis, there was a significant correlation with positive results for a treatment duration of six or more sessions. (70) Similar results have been obtained for tension headaches. (71) It should be noted, however, that this does not apply equally to all conditions and that a higher dose does not necessarily lead to a better effect, but may have the opposite effect. (72) Chen et al. conducted a meta-analysis and meta-regression analysis and came to the interesting conclusion that analgesic effects occurred with less than two acupuncture sessions per week, these effects were less pronounced with an

increase in frequency to two sessions per week, and a further increase to more than two sessions per week showed an improved analgesic effect. A similar result was obtained for treatment duration. With increasing duration per session, analgesia increased continuously up to a value of 30 minutes per session. After reaching this maximum, pain relief decreased with increasing treatment duration. (68) The reason for this discrepancy is probably due to the different mechanisms of action of acupuncture. As discussed in previous sections, the mechanism of action of acupuncture consists of different mechanisms that can occur locally, segmentally, centrally, and systemically. Presumably, different mechanisms are responsible for different clinical pictures. (73) Accordingly, it is necessary to investigate the dosage of acupuncture for cancer pain in order to explore the dose-response relationship for this area. When it comes to dosage, optimal effect is certainly a key factor. However, other factors also play a role in determining the importance of the dosage of acupuncture for tumor pain. Cancer patients suffer from severe physical stress and additional logistical problems. They often have to attend numerous doctor's appointments and undergo chemotherapy, which can be debilitating, and they often suffer from limited mobility and deteriorating physical condition. In this context, it would make sense to provide patients with a treatment that achieves optimal effects but does not cause additional stress and, above all, seems feasible. High intensity in the sense of several sessions per week would probably only be possible in an inpatient setting, and the options would have to be expanded accordingly. This thesis focuses on the dosage of acupuncture in terms of number of sessions, frequency, and duration of treatment with acupuncture for cancer pain in the form of a meta-regression. The meta-analysis in the first part also plays a key role, as it highlights the effect of different modalities through subgroup analysis. This thesis is a sub-analysis of a meta-analysis and meta-regression that examined the dosage of acupuncture for cancer pain, including pain caused by anti-cancer therapies such as RT, CT, and HT, among others. This thesis focuses entirely on cancer pain caused directly by the tumor itself and excludes other causes.

2. Methods

2.1. Methodology Choice

To address the research question, a systematic literature review was conducted to assess the efficacy of acupuncture in managing cancer-pain. Following this the quantitative synthesis of results was conducted using meta-analysis to evaluate the pooled effect of acupuncture on cancer-pain. The primary outcome was the change in pain intensity, measured by the mean difference (MD) on the numeric rating scale (NRS). The NRS is a tool for assessing the severity of pain at the moment, using a 11-point scale, with zero meaning “no pain” and ten standing for “the worst pain imaginable”. (74) Further outcomes respected were the brief pain inventory short form (BPI-SF), EORTC core Quality of Life Questionnaire (EORTC QLQ-C30) (75) and visual analog scale (VAS). BFI-SF assesses the pain severity, including the pain at the moment, the pain ‘at its worst’, ‘least’, and ‘average’ over the last 24 hours, using the NRS. BPI-SF also integrates the rating of interference of the pain with seven aspects of life: general activity, walking, normal work, relations with other people, mood, sleep, and enjoyment of life and the rating of release of pain felt from the current treatment. (74) The EORTC QLQ-C30 is a core questionnaire on the health-related QoL of cancer patients participating in international clinical trials. The EORTC QLQ-C30 comprises nine multi-item scales, including five functional scales measuring physical, role, cognitive, emotional, and social function, a global QoL scale and three symptom scales for fatigue, pain and nausea. There are also several individual items for assessing specific symptoms. These are rated in the form of a four-point scale, where one stands for “not at all” and four for “very strongly.” All scales and individual items

are then linearly transformed to a scale from zero to hundred for calculation purposes. (75,76) The VAS functions similar to the NRS, using a mostly a 10 cm line, with the left end points representing zero (“no pain”) and the right endpoint 10 (“the worst pain imaginable”). (77) Subgroup analyses were conducted to explore the differences in analgesic effect according to the type of acupuncture performed. This was followed by meta-regression to examine and assess the relationship between the number of acupuncture sessions, the duration of treatment (in weeks), and the intensity (sessions per week) on pain relief. Statistical significance was determined using a significance level of 0.05, that is a p-value less than 0.05 is considered statistically significant. Study heterogeneity was evaluated using the I^2 statistic. Statistical analyses were performed using R version 4.0.3 and the package “metafor” (78,79).

2.2. Search Strategy

The literature search was performed in the Medline(Ovid), EMBASE(Ovid) and Cochrane Central Register of Controlled Trials(Ovid) using the following search terms:

((cancer OR neoplasm OR carcinoma OR tumor OR tumour OR maligna*) AND (pain* OR analgesia OR analges* OR nocicept* OR neuropath*) AND (Acupuncture OR Meridians OR Electroacupuncture OR Moxibustion OR Auriculotherapy OR acupressure OR ear acupuncture OR ear acupressure OR acupuncture, ear OR acupuncture therapy OR moxa OR laser acupuncture OR seven star needle OR acupuncture analgesia OR acupuncture points OR electro-acupuncture OR electro acupuncture OR TENS OR transcutaneous nerve stimulation OR transcutaneous electric nerve stimulation OR transcutaneous electrical nerve stimulation OR electro-stimulation OR electro stimulation OR pharmacopuncture OR point injection)). All studies identified through this search were screened based on predefined inclusion and exclusion criteria. No additional filters for generating limits were used.

2.3. Inclusion and Exclusion Criteria

2.3.1. Study Inclusion Criteria:

- Randomized-controlled trials (parallel, cross-over design, or pragmatic)
- Condition: cancer pain or symptom control in cancer patients including pain
- Participants of either sex, 18 years, or older, histological confirmed diagnosis of cancer
- Manual (MA) or electrical acupuncture (EA) using needles on specific points on the body/ear.
- Control: Sham acupuncture (SA) (non-traditional acupuncture points), no treatment, usual care (UC), waiting list, active control (excluding acupuncture)
- Outcome measure: Patient-reported pain intensity or pain relief measurements (VRS, NRS, validated questionnaires)

2.3.2. Study Exclusion Criteria:

- Non-randomized trials, interim analysis, longitudinal follow-ups
- Condition: neuropathic pain, aromatase induced arthralgia, pain related to surgery
- Participants younger than 18 years
- Interventions not involving invasive needles including acupressure and transcutaneous electrical nerve stimulation (TENS) and other non-invasive techniques.
- Studies comparing different acupuncture styles

2.4. Data Extraction

Two reviewers (MH and MLS) independently extracted data on study characteristics, participants, interventions, controls, and outcomes. Discrepancies between reviewers were resolved by consensus. Data extraction focused on the number of acupuncture sessions, weeks of treatment, and patient-reported outcomes of pain reduction using validated scales such as the NRS. Results are shown in Table 1.

2.5. Quality Assessment

In accordance with the recommendations, two independent reviewers (MH and MLS) assessed the quality of the included trials. They analyzed the methodological components separately using the Cochrane Handbook for Systematic Review of Intervention, Version 6.5. The following components were assessed: the randomization process, deviations from the intended interventions, missing outcome data, the measurement of the outcome, the selection of the reported outcome, and the “overall risk of bias”. (80)

3. Results

3.1. Search Results and Study Description

The systematic literature search initially identified 5,318 records in the selected databases. After removing 1,347 duplicate entries, a total of 3,971 records were screened based on their titles and abstracts. During this screening process, 3,834 studies were excluded because they did not meet the selection criteria. Reasons for exclusion included animal model studies (n = 19), inappropriate intervention type (n = 134), language limitations (n = 420), failure to meet outcome criteria (n = 124), ineligible participant criteria (n = 152), publication type (n = 415), and non-randomized controlled trial (RCT) design (n = 2,570).

After initial screening, 137 full-text articles were evaluated for eligibility. Of these, 107 articles were excluded for the following reasons: duplication (n = 79), non-RCT design (n = 5), inappropriate control group criteria (n = 22), failure to meet outcome criteria (n = 6), withdrawn papers (n = 1), and language barriers (n = 6). Finally, 14 trials were included in the final qualitative review and meta-analysis. These trials investigated the effect of acupuncture on cancer-related pain and represent a comprehensive exploration of the available evidence.

The study selection process is illustrated in Figure 2 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (81).

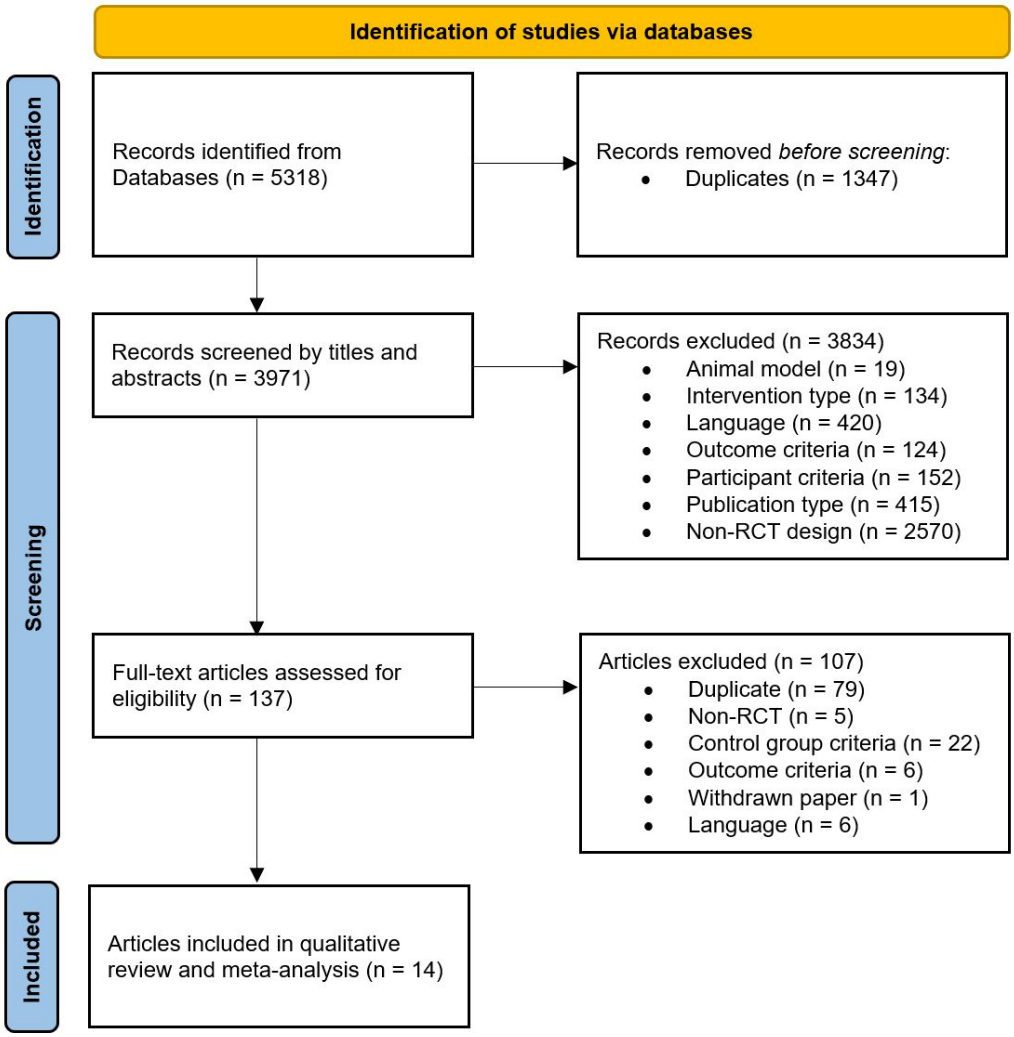

Figure 2: PRISMA Flow Chart. n: number of studies

3.2. Study Characteristics

3.2.1. Patients

A total of 368 patients were treated with MA, EA, and/or AA. MA is the traditional form of acupuncture in which the needle is manipulated manually by rotating, lifting, and thrusting, with the exact technique depending on the indication. EA uses direct current pulses instead of manual stimulation, transmitted to the needles by a specially designed device. (41,82) AA is also a traditional form of acupuncture that uses stimulation of points on the ear to regulate pain and

dysfunction. (83) While 404 patients received SA (182)(84–89), cognitive behavioral therapy (CBT) (115) (90,91), UC (93) (92–96), or analgesics (14) (97). SA as a control intervention includes various forms such as non-penetrating needling, shallow needling at either acupuncture points or non-acupuncture points, non-penetrating needling, and sham manipulation with devices. (98) All studies were published between 2003 and 2023. Table 1 provides an overview of the characteristics of the included studies.

Author (Year)	**N (A/C)**	**Intervention**	**Control**	**Cancer**	**Setting**	**Pain level**	**Outcome**	**Risk of bias**
Garland et al. (2019)	80/80	MA+AA	CBT	All cancer	Survivor	all	BPI-SF severity	low risk
Zhang et al. (2023)	69/69	EA+AA	SA	Breast	Remission	all	BPI-SF severity	high risk
Zhu et al. (2022)	19/19	EA	UC	Gastric	All	all	NRS	high risk
Yang et al. (2021)	35/35	MA	CBT	All cancer	Survivor	all	BPI-SF severity	some concerns
Saraswati et al. (2020)	14/14	EA	UC	Cervical	Chemotherapy	moderate (NRS >3)	NRS	high risk

Saraswati et al. (2019)	21/16	EA	UC	Cervical	Cisplatin	all	NRS	high risk
Kim et al. (2018)	14/13	MA	SA	Advanced cancer	All	all	NRS	low risk
Chen et al. (2013)	30/30	EA	SA	Pancreas	All	moderate (NRS >3)	NRS	some concerns
Lu et al. (2012)	7/7	EA	SA	Ovarian	Chemotherapy	all	EORTC QLQ-C30	some concerns
Alimi et al. (2003)	28/51	AA	SA	All cancer	All	moderate (NRS >3)	VAS	low risk
He et al. (2021)	15/14	MA	Analgesics	All cancer	All	moderate (NRS >3)	NRS	high risk
Pfister et al. (2010)	28/30	MA	UC	Head-Neck	All	moderate (NRS >3)	NRS	high risk
Ruela et al. (2018)	11/12	AA	SA	All cancer	All	moderate (NRS >3)	NRS	low risk
Chen et al. (2023)	15/14	MA	UC	All cancer	All	moderate (NRS >3)	NRS	high risk

Table 1: Study Characteristics. N(A/C): number of patients in active and control group, MA: manual acupuncture; AA: auricular acupuncture; EA: electroacupuncture; SA: sham acupuncture; CBT: cognitive behavioral therapy; UC: usual care; BPI-SF: brief pain inventory short form; NRS: numeric rating scale; EORTC QLQ-C30: The immediate analgesic effect of acupuncture for pain: a systematic review and meta-analysis (75); VAS: visual analog scale

3.2.2. Interventions

The intervention types of the included studies were MA (85,90,91,93,94,97), EA (84,86,87,92,95,96) and AA (84,88–90). The number of acupoints used ranged from one to 13 (median: 7.0 acupoints), although the majority of studies used specific protocols. The duration of treatment ranged from one week to 18 weeks (median: 4.0 weeks), the total number of sessions ranged from three to 56 (median: 10.0 sessions), the number of sessions per week ranged from 0.83 to 7 (median: 2.33), and the duration of a session ranged from 20 to 30 (median: 30.0 minutes). In three cases of AA, the acupuncture needles remained permanent (85,88,89).

3.2.3. Control Interventions

The efficacy of acupuncture has been evaluated in two trials comparing it to CBT (90,91), in six trials by comparing it to SA (84–89), in five trials by comparing it to UC (92–94), and in one trial comparing it to analgesics (97).

3.2.4. Outcome Measures

The primary outcome was pain intensity as assessed by the BFI-SF (84,90,91), NRS (85,86,89,92–97), EORTC QLQ-C30 (87), and VAS (88). Outcome measures were normed to the NRS and MD was calculated.

3.2.5. Risk of Bias

Figure 3 shows the risk of bias among the included trials. All studies reported the use of randomization. One study used simple randomization (biased coin method) without specifying whether it was conducted manually or by computer (89). All of the other trials used computerized techniques to achieve randomization. A summary of the potential biases is provided below, based on the review authors'

assessment of each point.

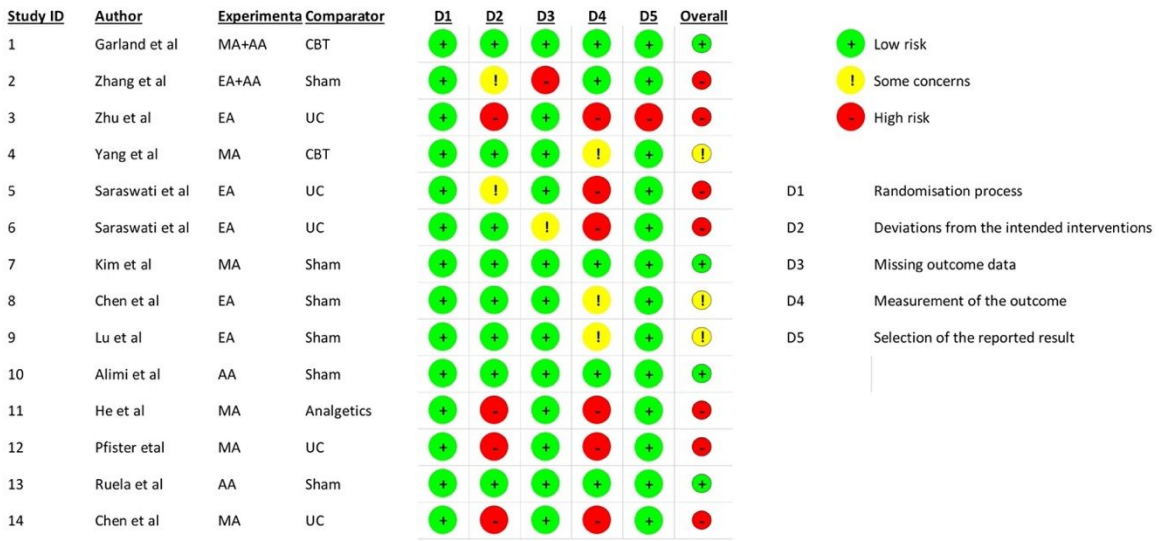

Figure 3: Risk of Bias. Green circles with a plus sign indicate that the methodological procedure was correctly executed and that there is a low risk of bias. Yellow circles with a question mark indicate that the authors did not describe the procedure and that the risk of bias is unclear. Red circles with a minus sign indicate that the procedure may have a high risk of bias.

The randomization process (D1) was adequately described in all trials (84–97), so the risk of bias was low. Six trials were found to deviate from the intended interventions (D2), giving rise to concerns in two trials (84,96) and a high risk of bias in four trials (92–94,97). In contrast, the remaining trials were considered to have a low risk of bias (85–90,95,99). Two trials had missing outcome data (D3), with one having a high risk of bias (84) and the other having some concerns (95). Conversely, the remaining studies had no cases of missing outcomes (85–90,92–94,96,97,99). With regard to the measurement of the outcome (D4), five trials were identified as having a low risk (84,85,88–90), three as giving some reason for concerns (86,87,99) and six as having high risk (92–97). The analysis

of the selection of reported results (D5), on the other hand, showed a low risk in thirteen cases (84–90,93–97,99). Overall, four studies had a low risk of bias (85,88–90), three studies had some concerns (86,87,99), and seven studies had a high risk of bias (84,92–97).

3.3. Meta-Analysis

A total of fourteen studies were conducted to evaluate the efficacy of acupuncture (Experimental) in reducing pain in cancer patients. These studies used a variety of control groups (Control), including CBT, UC, SA, and analgesics.

3.3.1. Acupuncture vs Control

The pooled MD across the studies was found to be -1.50 points on the NRS [95% confidence interval (CI): -2.41 to -0.60], with a p-value<0.01. This indicates that acupuncture significantly reduces cancer pain by an average of 1.50 points on the NRS when compared to the control group. Detailed results can be found in Figure 4, including the numbers of patients in each subgroup and intervention group, standard deviations (SDs), MDs, 95% CI and weight.

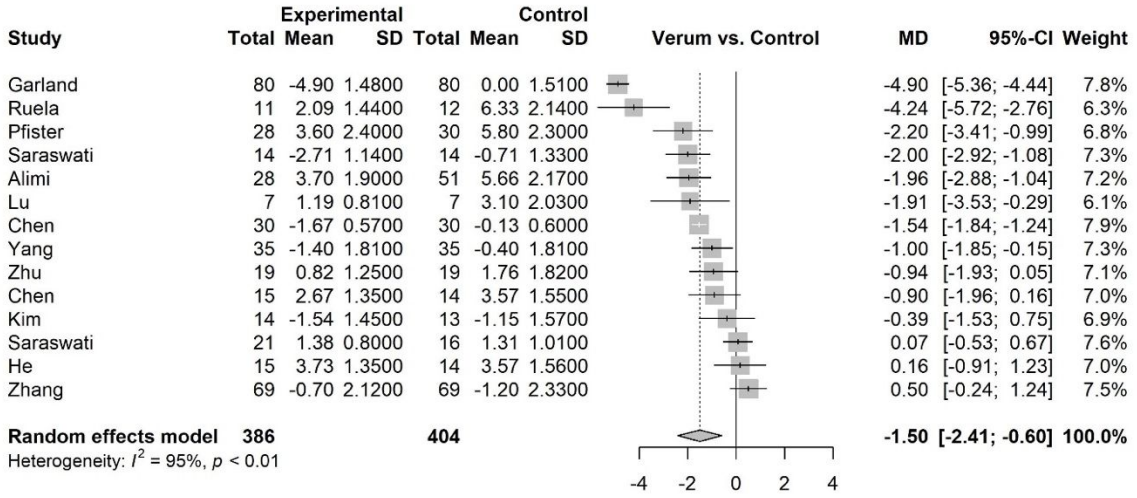

Figure 4: Forest Plot of Acupuncture (Experimental) vs Control. Outcome is MD: mean difference in pain intensity NRS, SD: standard deviation

As indicated in the extant literature, a minimally important difference in cancer pain reduction on the NRS is estimated to be between -1.4 and -1.9 points. Given the pooled MD of -1.50, acupuncture is associated with clinically relevant pain relief, as it falls within the range of minimally important differences for cancer pain. (100) However, there was considerable heterogeneity between the studies, as indicated by an I^2 value of 95% and a p-value that suggests statistically significant heterogeneity ($p<0.01$). This indicates a considerable degree of variability in the observed effect sizes across the studies. The heterogeneity was investigated and may be explained by the type of acupuncture used. Therefore, a subanalysis was performed for different acupuncture interventions.

3.3.2. Meta-Analysis Subgroups

The objective of the subgroup meta-analysis was to investigate the effectiveness of different acupuncture interventions. The subgroups analyzed included five trials using manual acupuncture (MA) (85,93,94,97,99), five trials using EA (86,87,92,92,95), two trials using AA (88,89), one study combining MA and AA (MA+AA) (90) and one combining EA and AA (EA+AA) (84) for the reduction of cancer pain. Figure 5 illustrates the detailed results of the subanalysis.

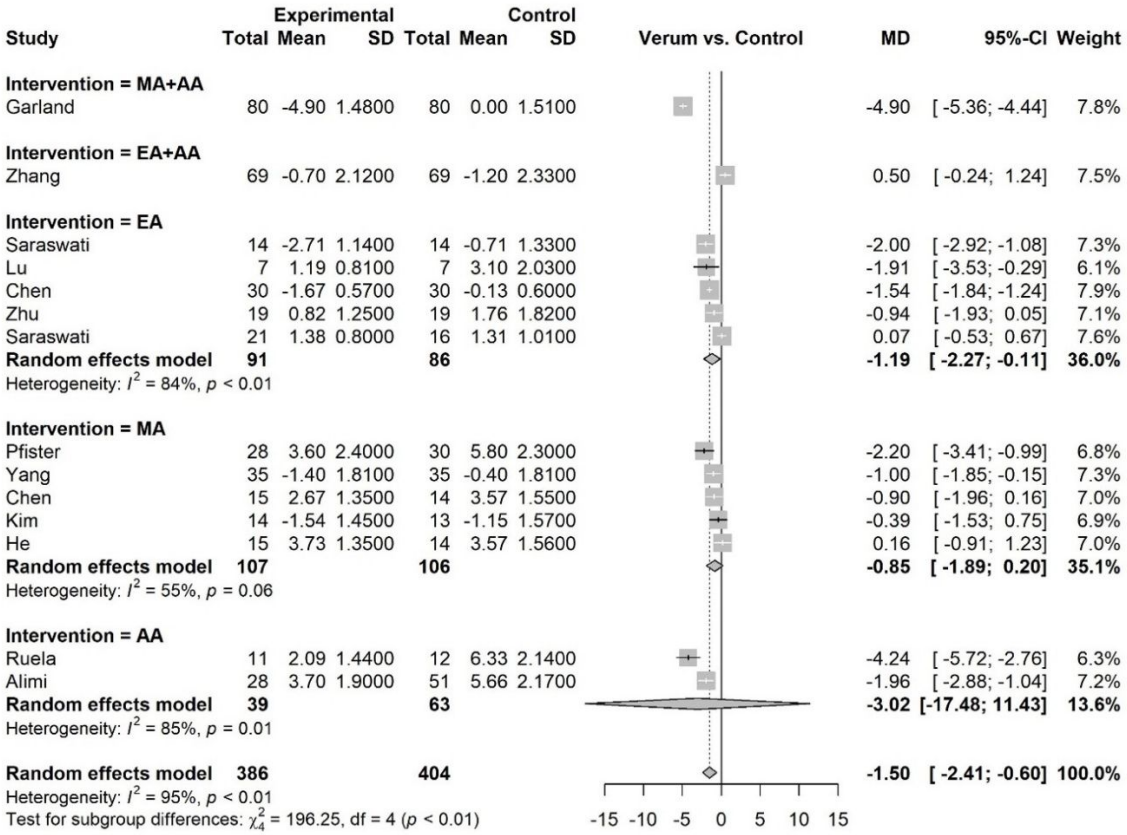

Figure 5: Forest Plot of the Subgroup-Analysis of Acupuncture Interventions. χ2: chi-square-test; df: degrees of freedom

The subgroup combining MA and AA was represented by only one trial by Garland et al. It showed an MD of -4.90 [95% CI: -5.36 to -4.44], indicating a large reduction in pain (90). In contrast, the results of the other subgroup, which investigated combined techniques, using MA and AA suggested a much smaller effect with an MD of 0.50 [95% CI: -0.24 to 1.24]. (84) However, the two subgroups investigating combined interventions were represented by only one trial each. The pooled estimate for EA was -1.19 [95% CI: -2.27 to -0.11], indicating a moderate effect of EA on cancer pain reduction. There was still significant heterogeneity in the subgroup with an I^2 of 84% ($p<0.01$) in the EA group, indicating substantial variability between trials. This suggests that the results of the individual trials are not fully consistent and that there may be other factors that influence the effect of EA. Studies in the MA subgroup generally showed moderate

effects on pain reduction. The pooled estimate was -0.85 [95% CI: -1.89 to 0.20], indicating a weaker effect of MA compared to other types of acupuncture. The degree of heterogeneity in this group was moderate, with an I^2 value of 55% (p=0.06), indicating some variability in the effect sizes, although not as pronounced as in the EA subgroup. The subgroup analyzing trials using AA showed a large reduction in pain. The pooled estimate for this subgroup was -3.02 [95% CI: -17.48 to 11.43], indicating that AA appears to have the largest effect on cancer pain reduction. However, there was considerable heterogeneity between the two studies in this subgroup, with an I^2 of 85% (p=0.01), suggesting that the results may not be fully reliable.

A χ^2 test for subgroup differences produced a value of 196.25 (degrees of freedom (df) = 4, p<0.01), indicating that there are statistically significant differences between the effects of the different acupuncture interventions (MA, EA, AA, and combined approaches).

3.4. Meta-Regression

The purpose of the meta-regression was to investigate the relationship between the number of acupuncture sessions, number of weeks and intensity (ratio session per week) and the amount of pain reduction (mean difference) in cancer patients.

3.4.1. Number of Sessions

The first meta-regression analyzed the relationship between the number of acupuncture sessions and the reduction of cancer pain. The results showed a beta coefficient of -0.06 points on the NRS ([95% CI: -0.12 to 0.00], p=0.05). The overall model p-value was p<0.0001, indicating that the model used had significance. The results showed that for each additional session of acupuncture, the MD in pain score decreased by 0.06 points, suggesting that more sessions are associated with greater pain reduction. However, the result was not statistically significant. Figure 6 illustrates the results and Table 2 offers a detailed overview of the analysis results.

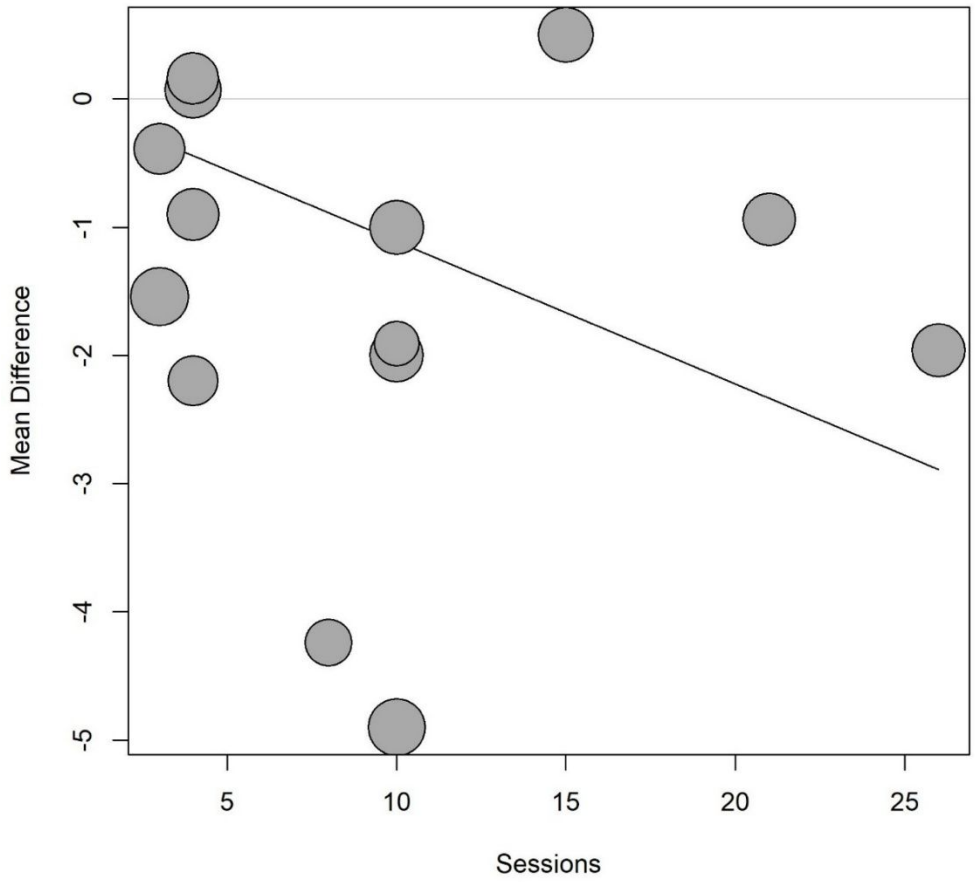

Figure 6: Meta-Regression of Number of Sessions. Bubble sizes represent the weight of each trial in the meta-regression

Variable	Beta	Std. Error	t-value (df)	95% CI	p-value
Sessions	-0.06	0.03	-2.15 (13)	-0.12; 0.00	0.05

Table 2: Meta-Regression of Number of Sessions. Std. Error: standard error, df: degrees of freedom, CI: confidence interval

3.4.2. Number of weeks

The objective of this meta-regression analysis was to investigate the relationship between the duration of the acupuncture treatment in weeks and its effect on cancer pain reduction. Figure 7 illustrates the relationship between the variables. The p-value for the overall model examining the relationship was p<0.0001, indicating that the overall model was significant. The beta coefficient for number of weeks was -0.16 ([95% CI: -0.31 to -0.02], p=0.03), indicating that for each additional week of acupuncture treatment, pain scores on the NRS significantly decreased by 0.16 points. This suggests that longer treatment periods are associated with greater reductions in cancer pain. Table 3 provides a detailed overview of the results.

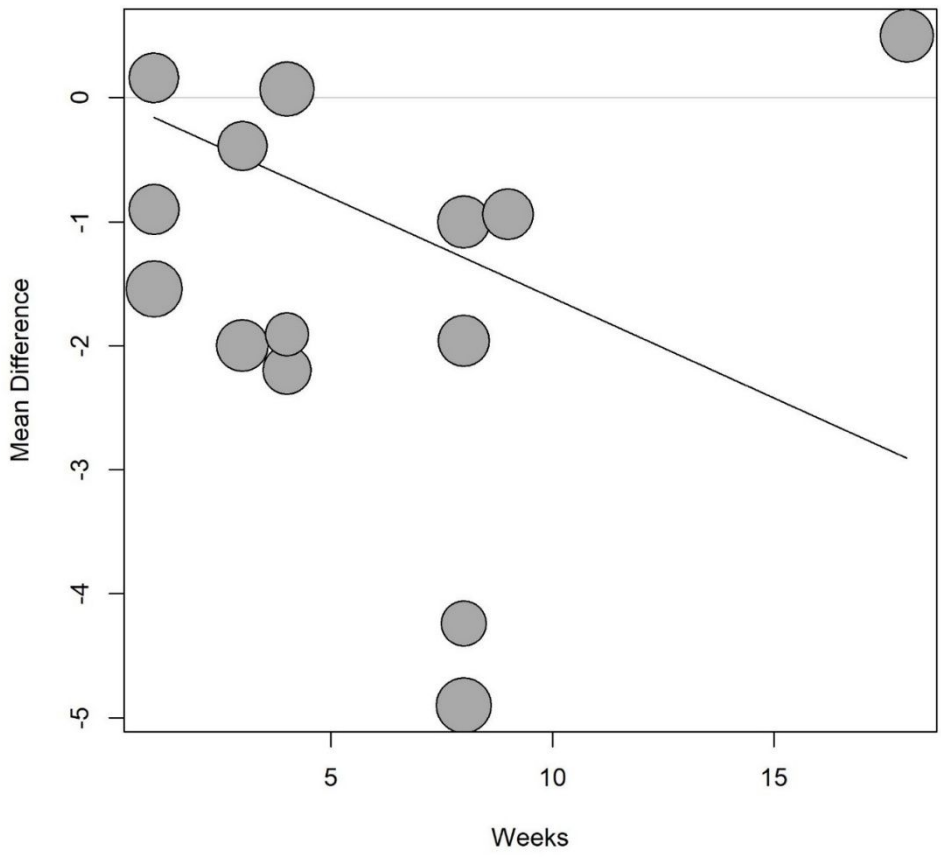

Figure 7: Meta-Regression of Number of Weeks. Bubble sizes represent the weight of each trial in the meta-regression

Variable	Beta	Std. Error	t-value (df)	95% CI	p-value
Weeks	-0.16	0.07	-2.39 (13)	-0.31; -0.02	0.03

Table 3: Meta-Regression of Number of Weeks

3.4.3. Intensity

The purpose of this meta-regression analysis was to examine the effect of acupuncture treatment intensity, measured by the ratio of sessions per week, on cancer pain reduction. In Figure 8, the correlation between the two variables is visually represented. The overall model again showed significance with a p-value $p<0.0001$. The beta coefficient for intensity was -0.40 ([95% CI: -0.76 to 0.04], $p=0.03$), indicating a significant effect of intensity on pain reduction. The results suggest that increasing the intensity of acupuncture may lead to a greater reduction in pain scores on the NRS. The detailed results are shown in Table 4.

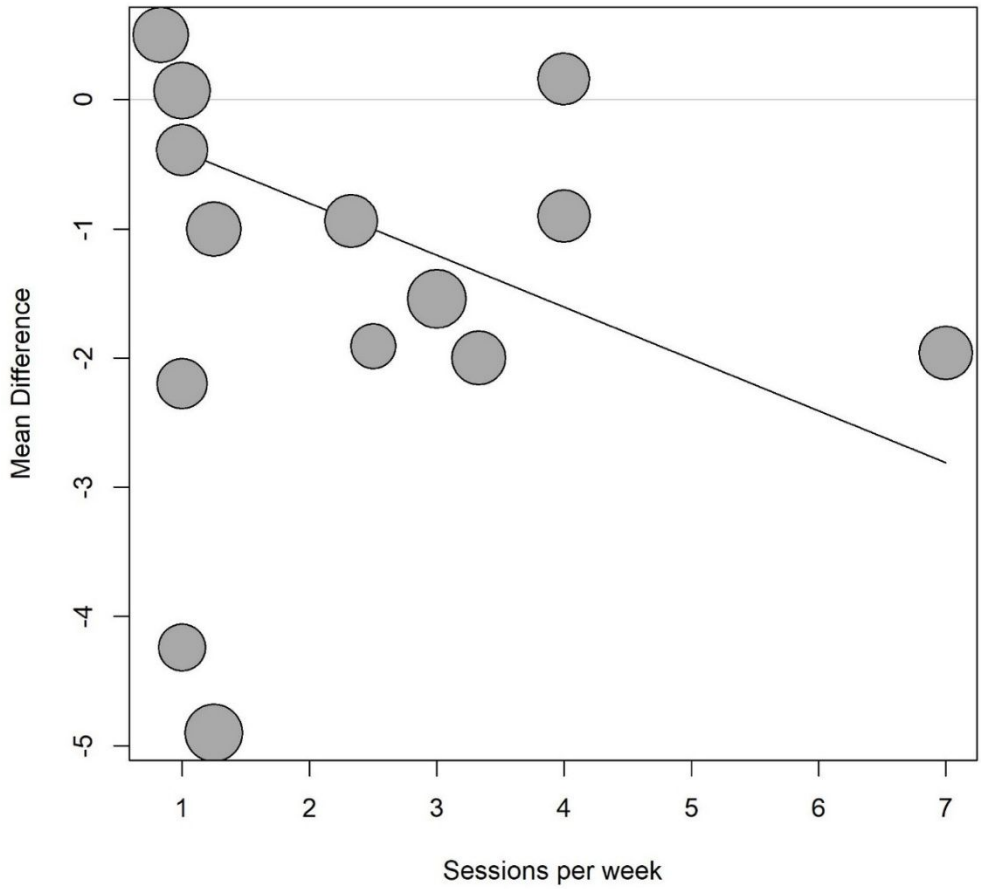

Figure 8: Meta-Regression of Treatment Intensity (sessions per week). Bubble sizes represent the weight of each trial in the meta-regression

Variable	Beta	Std. Error	t-value (df)	95% CI	p-value
Sessions/week	-0.40	0.16	-2.40 (13)	-0.76; 0.04	0.03

Table 4: Meta-Regression of Treatment Intensity, Std. Error: standard error, df: degrees of freedom, CI: confidence interval

3.4.4. Multiple Regression

The objective of the multiple regression model was to investigate the relationship and interaction of the number of sessions and weeks, sessions*weeks on cancer pain reduction. The overall model p-value of 0.12 indicates that the multiple regression model did not reach statistical significance when all the variables were considered together. However, the individual variables showed significant results and suggest that there are trends. The results of the analysis are displayed in Table 5.

Variables	Beta	Std. Error	t-value (df)	95% CI	p-value
Sessions	-0.41	0.15	-2.71 (10)	-0.74; -0.07	0.02
Weeks	-0.53	0.22	-2.37 (10)	-1.02; -0.03	0.04
Sessions*Weeks	0.05	0.02	2.68 (10)	0.01; 0.10	0.01

Table 5: Multiple Regression, Std. Error: standard error, df: degrees of freedom, CI: confidence interval

Increasing the number of sessions and keeping the number of weeks constant resulted in a significant reduction in pain score of -0.41 ([95% CI: -0.74 to -0.07], p=0.02). Increasing the number of weeks while keeping the number of sessions constant also had a significant effect, showing a pain reduction of -0.53 ([95% CI: -1.02 to -0.03], p=0.04). The interaction of sessions and weeks of sessions*weeks showed a significant synergistic effect with an improvement in effect of 0.05 ([95% CI: 0.01 to 0.10], p=0.01).

3.5. Assessment of Publication Bias

Figure 9 presents a funnel plot for assessing publication bias. The symmetrical distribution of studies on both sides of the funnel, including those with non-significant results, indicates that both significant and non-significant findings are

represented in the published literature and that there is no evidence of publication bias.

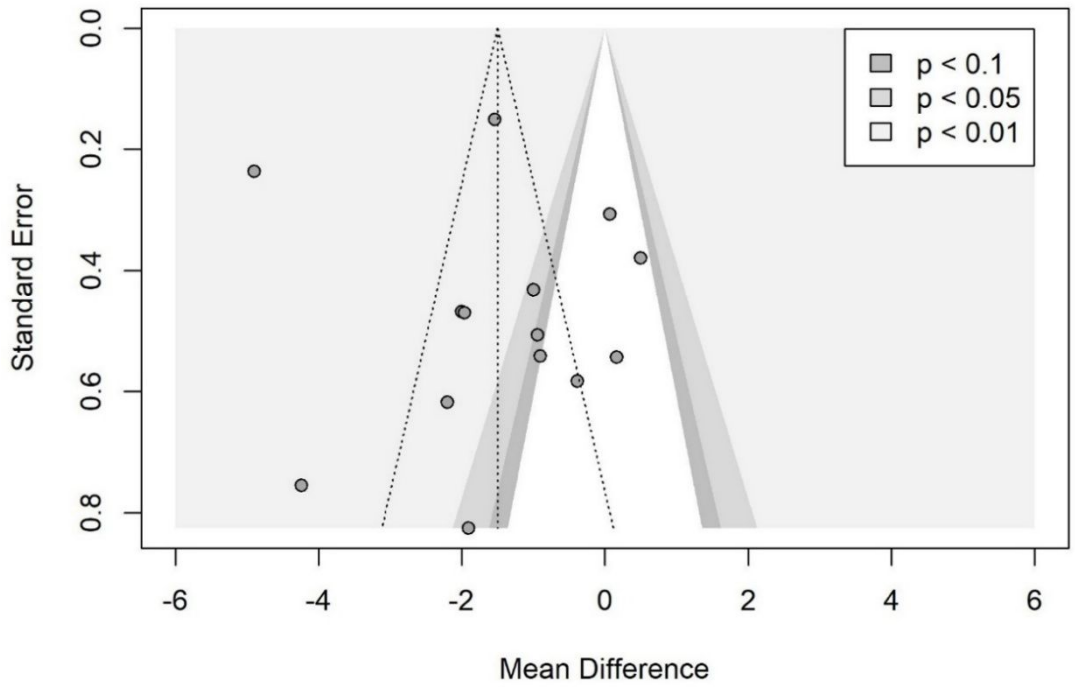

Figure 9: Funnel Plot for Assessing Publication Bias. Each data point on the plot represents a single study, with the x-axis indicating the mean difference (MD) in cancer pain reduction and the y-axis representing the standard error, which serves as a measure of study precision. The plot indicates that larger, more precise studies (with smaller standard errors) are located toward the top of the plot, while smaller, less precise studies (with larger standard errors) are plotted toward the bottom. x-axis: MD in cancer pain reduction; y-axis: standard error; dark grey: p-value <0.1; intermediate grey: p-value <0.05; white: p-value < 0.01; dotted lines: confidence interval around MD

4. Discussion

4.1. Results and Comparison to Other Findings

This thesis presents a study that investigated the pain-relieving efficacy of acupuncture and specific acupuncture modalities and the effect of acupuncture

dosage on cancer-related pain using a systematic review, meta-analysis, and meta-regression. A total of 14 RCTs and a total patient population of 772 individuals diagnosed with cancer and experiencing tumor-related pain were included in the study. The meta-analysis showed a statistically significant reduction in pain intensity with a mean reduction of -1.50 points [95% CI: -2.41 to -0.60; $p<0.01$; $I^2= 95\%$] on the NRS scale compared to the control groups.
The analyses of subgroups categorized by intervention type and their combinations showed a statistically significant difference between the different intervention groups. The combined intervention with MA+AA acupuncture, although represented by only one RCT (90), showed the most pronounced effect with an MD of -4.90 points [95% CI: -5.36 to -4.44]. The subgroup of combined EA+AA demonstrated a relatively modest effect with an MD of +0.5 points [95% CI: -0.24 to 1.24]. This finding was also represented by a single study (84), which prevented the application of heterogeneity analysis to the combined intervention subgroups. The AA group showed a decrease of -3.02 [95% CI: -17.48 to 11.43], indicating that AA has the largest effect in pain reduction. However, the analysis of heterogeneity showed an I^2 of 85% ($p<0,01$) and the 95% CI had a very wide range, indicating high variability between the included trials. The EA subgroup showed a moderate effect on pain reduction, with an MD of -1.19 [95% CI: -2.27 to -0.11], while the smallest effect was observed in the MA group, an average decrease of -0.85 [95% CI: -1.89 to 0.20]. The difference in analgesic efficacy between MA and EA is already the subject of research. Some studies suggest that EA has a much better analgesic effect than MA. (43,101–103) The exact underlying mechanisms are not yet clear, but there are explanatory approaches that still need to be substantiated. Zheng et al. found in an RCT on pain-free patients that EA at 2/100 Hz could cause a significant increase in two different types of pain thresholds. MA also had a positive effect, but EA was much faster and stronger. In addition, it was found that the analgesic effect of EA occurred within 30 minutes after the intervention and lasted for at least 24 hours, which could indicate a dual mechanism of action involving a fast-acting neuronal component and a long-lasting neuronal-humoral component. Central and

peripheral mechanisms, including the involvement of endogenous opioid peptides, and activation of the pain-inhibiting system, presumably play a role here. (104) As mentioned in the section on the central mechanisms of acupuncture, there are differences in the release of endogenous opioids. It has been shown that 2 Hz EA leads to the release of enkephalin, β-endorphin and endomorphin, whereas 100 Hz EA specifically stimulates the release of dynorphin. When the two frequencies are combined, all four opioid peptides are released simultaneously and bind to μ-, δ- and κ-receptors, making the effect of EA similar to that of codeine, which also binds to μ- and δ-receptors. This may be an important reason for the superior efficacy of EA. (40,104) There is also evidence that the activation of endogenous peptides by EA may have non-specific inhibitory effects on wind-up, which is an important factor in pain sensitization. (104) An early finding was that the application of naloxone could abolish the effect of acupuncture analgesia in animals and humans, suggesting the involvement of the endogenous opioid system in its mechanism. (38,105) further studies found that only the analgesic effect of low-frequency EA could be blocked, but not that of high-frequency EA, suggesting the involvement of a different mechanism. (106) Further studies led to the discovery that EA has an influence on LTD and long-term potentiation (LTP) of neuronal plasticity. In experiments on rats with neuropathic pain, Xing et al. found that 2 Hz EA induced LTD in C fiber evoked field potentials in the dorsal horn of the spinal cord. This LTD could be reversed by the opioid antagonist naloxone. (107) However, 100Hz EA induced LTP in the same rats, whereas it induced LTD in control rats. Both phenomena were weakened by GABA or 5-HT receptor antagonists. (108) This suggests that EA has a modulating effect on LTD and LTP of neuronal plasticity and may have an analgesic effect on neuropathic pain. (82,108) These phenomena may also explain the long-lasting effects of acupuncture. (82) The results of some studies suggest that the analgesic effect of EA is mainly due to the activation of Aβ/δ fibers, whereas the effect of MA is mainly due to C fibers. (22) A study by Napadow et al. investigated the central effects of EA compared to MA using fMRI. Compared to placebo-like tactile control stimulation, both acupuncture techniques (EA and MA) showed an increase in the

hemodynamic signal in the anterior insula and a decrease in areas of the CNS, such as the limbic and paralimbic structures with AMYG and anterior hippocampus, frontal and temporal poles. This suggests that the corticolimbic network may have an substantial effect on the modulatory effects and clinical efficacy of acupuncture. (41) In contrast, only EA stimulation showed a significant signal increase in the anterior middle cingulate cortex and at 2 Hz in the pontine raphe area. EA induced more widespread signal increase than MA. This indicates differences in the effects on the CNS and the mechanisms of action triggered by the different techniques, which may explain the differences in the effect sizes. (41) However, significant heterogeneity was still observed among the included trials in the subgroups. The EA group showed an I^2 of 84% ($p<0.01$), suggesting that other factors may have influenced the results. This is also applicable to the AA group (I^2=85%, p=0.01), which shows significant results for heterogeneity, and the MA group (I^2 = 55%, p=0.6), although it was not significant for this group. However, this leaves the possibility that other mechanisms or factors, such as differences in methodology, patient groups or control interventions, may have influenced the results.

The results of our meta-analysis showed that acupuncture interventions could significantly reduce tumor pain compared with control groups. A meta-analysis conducted by Choi et al. also investigated the analgesic efficacy of acupuncture in cancer patients. The results did not show superiority of acupuncture compared with conventional drug therapy (risk ratio (RR), 1.12, [95% CI: 0.98 to 1.28], p=0.09; I^2=67%). When comparing acupuncture combined with drug therapy to drug therapy alone, the meta-analysis was able to show significantly superior effects of acupuncture (RR, 1.36, [95% CI: 1.13 to 1.64], p=0.003; I^2=70%). Compared to SA, the meta-analysis could not show that acupuncture had significant effects on pain reduction with a SMD of -0.41, ([95% CI: -1.39 to 0.49], p=0.37). The trials in the meta-analysis included multiple acupuncture techniques and no subgroup analyses were performed to examine their effects, although there was significant heterogeneity. In addition this meta-analysis included a total number of three trials with overall high risk of bias. (64) The results of this meta-

analysis do not align with the results this meta-analysis. A meta-analysis conducted by Faria et al. on patients with various types of painful conditions was able to demonstrate the analgesic efficacy of acupuncture. (66) The study examined the effects of acupuncture compared to no treatment (SMD: -0.90, [95% CI: -1.68 to -0.12] p=0.003; I^2=83%), compared to SA (SMD: -1.10, [95% CI: -1.59 to -0.61], p<0.00001; I^2=81%), and compared to UC (SMD: -1.16, [95% CI: -1.38 to -0.93], p<0.00001; I^2=43%). In the subanalysis of acupuncture versus no treatment, both MA and EA showed a significant pain-reducing effect (SMD(MA): -0.61, [95% CI: -0.97 to -0.24], p=0.32; I^2=0%) and (SMD(EA): -1.65, [95% CI: -2.15 to -1.14], p<0.00001), with EA being significantly more effective. No AA trials were included in the analysis. (66) When comparing acupuncture with SA, MA showed a moderate effect (SMD: -0.75, [95% CI: -1.12 to -0.39], p=0.08; I^2=56%), while EA (SMD: -1.29; 95% CI: -2.50 to -0.08, p = 0.0003; I^2=88%) and AA (SMD: -2.22; 95% CI: -3.30 to -1.14; p < 0.0001) showed a large effect. When controlled against UC, MA again showed a moderate effect (SMD: -0.78; 95% CI: -1.21 to -0.34, p = 0.37; I^2=0%) and EA (SMD: -1.27; 95% CI: -1.27 to -0.92); p = 0.13; I2 = 56%) and AA (SMD: -2.32; 95% CI: -1.71 to -0.93; p > 0.00001) a stronger effect. In both cases, AA had the strongest effect. Thus, the results of Faria et al. are comparable to ours and confirm the efficacy of acupuncture, with AA appearing to have the greatest efficacy and MA showing a significant reduction in pain but the most moderate effect. (66) He et al. came to the same conclusion, although this analysis included acupressure as a form of intervention and interventions combined with analgesics that were conducted as open-label studies. Aim was to investigate acupuncture´s efficacy on reducing cancer pain, including postoperative and aromatase inhibitor-induced pain. The analysis has its main focus on comparing the effect sizes of acupuncture interventions depending on different control groups. (65) However, subgroup analyses of blinded studies were performed, which analyzed trials that compared true acupuncture with SA. In this analysis, MA, EA, and AA were considered true acupuncture. The results of this subanalysis showed a reduction in pain with acupuncture interventions, with an MD of -1,38 points ([95% CI: -2.13 to -0.64]; I^2 = 81%). (65) The greatest effect

was achieved by AA (MD: -2.98, [95% CI: -5.37 to -0.59]; I^2 = 84%), which is consistent with our findings. MA followed with a moderate pain-relieving effect (MD: -0.88, [95% CI: -1.75 to -0.01]; I^2 = 59%). The least effective compared to the other interventions was EA with an MD of -0.84 [95% CI: -2.43 to 0.75]; I^2 = 84%). EA, being the least effective intervention type, represents a deviation from our findings. However, the results of meta-analysis reporting the efficacy of acupuncture in reducing cancer-related pain and the superiority of AA are consistent with our results. (65) Dai et al. conducted a meta-analysis that examined the efficacy of acupuncture and related therapies for pain management in a palliative cancer setting. The analysis included single-arm and controlled trials and also searched Chinese databases for eligible studies. The analysis of the trials also showed a significant effect of acupuncture and its derivatives with a reduction in NRS pain score of -1.33 (WMD, [95% CI: -0.85 to -1.82], p<0.001). (67) The acupuncture group included interventions, such as TENS, intradermal acupuncture, MA, EA, AA, wrist-ankle acupuncture, electrothermal acupuncture, and fire needling. The subanalysis showed a significant pain reduction for all acupuncture types mentioned except for TENS and intradermal acupuncture. Again, MA showed a moderate effect with a pooled MD of -0.90 ([95% CI: -0.64 to -1.15], p<0.001), as did EA with a WMD of - 1.18 ([95% CI: -0.63 to -1.72], p<0.001). Again, AA had the strongest effect, with a WMD of -5.60 [95% CI: -4.33 to -6.88], by far the largest effect size. The order of the interventions by effect size is consistent with our findings. (67) Another meta-analysis by Chiu et al. also found that acupuncture reduced cancer pain. However, the study included other types of tumor-related pain in addition to the pain by the tumor itself, including also pain caused by CT, RT, HT, and surgery. It also included two studies that investigated moxibustion and TENS as part of the interventions group. (26) Although the subgroup analysis of this study specifically focused on different types of pain and the efficacy of the different interventions was not analyzed, the results showed that acupuncture was not effective in treating CT-, RT-, or HT-induced pain, but it could achieve successful pain relief for surgical and tumor-related pain. The analysis of the trials examining the reduction of cancer pain showed a WMD of -0.71 ([95%

CI: -0.94 to -0.48], p< 0.0001; Cochran's Q statistics: 24.39, I^2=34,41%, p=0.08), indicating that acupuncture significantly relieved cancer pain, which is consistent with our finding. (26)

Given the potential analgesic effects of acupuncture on cancer pain, the effect of different acupuncture doses was investigated. Therefore, a meta-regression was performed to examine the relationship between pain reduction based on the mean reduction in points on the NRS pain scale and the number of acupuncture sessions, the number of weeks of treatment, and the intensity. In general, the results indicate a progressive decrease in pain intensity with increasing number of sessions (beta: -0.06, [95% CI: -0.12 to 0.00], p=0.05), number of weeks (beta: -0.16, [95% CI: -0.31 to -0.02], p=0.03], and intensity (sessions/week) (beta: -0.40, [95% CI: -0.76 to 0.4], p=0.03]. All three models showed clear significance (overall model significance p<0.0001), and each meta-regression presented an inverse relationship of the dosage. While the meta-regression for weeks produced no statistically significant result, the results for weeks and intensity showed significance. The use of multiple regression did not provide an overall model significance (p=0.12). This is likely due to the variability observed in the conduct of the trials, which introduced considerable heterogeneity. Nevertheless, the results of this study indicate a trend whereby both the number of weeks and the number of sessions is associated with increased pain reduction. In addition, more intensive treatment (i.e., more sessions per week) was found to intensify the reduction in tumor pain due to a synergistic relationship between weeks and sessions.

A study by Xu et al. examined the dose-response relationship in major depressive disorder (MDD) using a robust-error meta-regression. The dose was determined only by the number of sessions, and an attempt was made to approximate the nonlinear relationship using a restricted cubic spline. The outcome used was the Hamilton Depression Rating Scale (HAMD) score, a quantitative score for measuring symptoms of MDD. The analysis showed a V-shaped relationship between the number of sessions and the HAMD score, indicating a relationship between the number of sessions and improvement in the HAMD score. There was a significant improvement between 18 (0.41, [95% CI: 0.36 to 0.47]) and 28

sessions (0.59, [95% CI: 0.53 to 0.65]). A peak was found at 36 sessions (0.66, [95% CI: 0.59 to 0.72]), after which the rate of improvement even decreased slightly from 0.66 [95% CI: 0.59 to 0.72] to 0.55 [95% CI: 0.35 to 0.76]. Thus, this analysis shows a plateau at 36 sessions. The V-shaped correlation in this study differs from the linear relationship in our analysis but is consistent with the correlation between number of sessions and outcome. This analysis does not provide evidence for an influence of session length or treatment intensity. (109) A large meta-regression is the FAMOUS study, which examined the influence of various factors on the effect of acupuncture, including the frequency of sessions. Eligible outcome criteria were categorized into six different constructs using RCTs´ protocols, one construct being pain. The meta-regression analyses used SMDs as effect estimate for the dependent variable. In addition to univariable meta-regression, multivariable meta-regression was included using a three-level robust mixed model. The analysis showed that a higher frequency of sessions was associated with a better outcome (SMD: 0.19, [95% CI: 0.03 to 0.35], p=0.02). (110) A similar study was conducted, also using outcome data reported in trials and integrating them into a construct group, such as pain. A multivariable analysis was conducted for the pain construct, including 14 variables. As an effect estimate for the dependent variable difference in adjusted SMDs was used. The analysis showed that for the pain construct the only variable that demonstrated a significant association with the magnitude of outcome was the frequency of treatment sessions (difference in adjusted SMDs: 0.46, [95% CI: 0.07 to 0.84], p=0.02) showing better outcomes in high frequency treatments than in low frequency treatments. In contrast, no significant association for the duration and the total number of treatments was found. (111) MacPherson et al. conducted a meta-regression with almost 18,000 patients suffering from various pain disorders, such as non-specific back or neck pain, shoulder pain, chronic headache, or osteoarthritis. The analysis examined the influence of various factors on the effect of acupuncture. These factors included type of acupuncture, point prescription, needle placement, use of electrical stimulation and moxibustion, presence of acupuncture-specific patient-practitioner interactions, acupuncturist experience,

number of needles used, and number, frequency, and duration of sessions. (112) The analysis at the patient level showed that a higher number of sessions could improve the effect of acupuncture with a beta of 0.11 per 5 sessions ([95% CI: 0.01 to 0.21], p=0.0007]) compared to the control group without acupuncture. The result of MacPherson et al. thus correlates with our finding that an increase in the number of sessions can lead to a better effect. However, in contrast to our analysis, there was no correlation with the duration or frequency of acupuncture. (112) In conclusion, this study suggests that acupuncture is an efficient method for managing tumor pain and indicates that dosage may play a role in determining the extent of pain reduction.

4.2. Limitations

While the results of this study are promising, it is important to be aware of the limitations of this study. A limitation of this analysis was that several included trials had a moderate or high risk of bias. Some studies exhibited deficiencies in the measurement of outcomes. The objective translation of pain into outcome measures is a challenging task. Pain is a subjective experience that is influenced by a variety of factors, which inherently makes it difficult to measure in a value-free manner. Pain intensity reflects not only the nociceptive component, but also the perception of pain, which is influenced by culture, beliefs, mood or delirium, and a variety of other symptoms experienced by patients with cancer pain, such as fatigue, anorexia, cachexia, chronic nausea, dyspnea, anxiety, and depression. Their influence is often not taken into account. (4) With regard to assigning value to pain, Goldman et al. gathered interesting observations through surveys of health care providers. They found that patients often struggle using numerical scales. As a result it was observed that patients continued to report high pain intensity even when other indicators suggested that pain had improved, because they continued to identify themselves as a person with severe pain. In addition, patients seemed to remember severe pain more easily than mild pain. Relatedly, patients showed difficulty with questions about their pain that had a temporal component, such as average pain, or the relationship to activity. (113) Another

limitation of this analysis was the challenge that acupuncture shares with all non-pharmacological trials, namely the difficulty of blinding. A resulting problem is that both the patient's and the practitioner's expectations have an effect and thus may influence the outcome. (114,115) Placebo interventions provide the opportunity to blind patients, but an ideal placebo has not yet been found. SA as a placebo is one of the most popular control interventions and has been used in many variations. However, no ideal method has been found that is indistinguishable from real acupuncture. (115) A number of studies, however, in which patients were asked after the interventions whether they thought they had received real acupuncture or SA have been successfully blinded. (116–119) One of these studies was conducted by Streitberger et al., who introduced and evaluated a new SA device. The results suggested that successful blinding using this device was achievable. Several RCTs included in this analysis used this very tool, known as Streitberger needle, for SA. (119) Nevertheless, there is also some evidence that SA may have an effect, e.g. by activating the DNIC, influencing the results of studies and making interpretation of clinical results difficult. (120,121) Control interventions and their influence play an important role. This analysis, however, did not address the differences in effect sizes related to different control interventions, which could have contributed to heterogeneity. Another factor contributing to the bias of some trials in this analysis is the deviation from the planned interventions in some studies. As a result, the trials are of lower quality and the results are difficult to interpret. To avoid this, clear protocols for the implementation of the interventions would be a crucial help. (68) A perspective on how this could be achieved is outlined in the section on implications for further research. Another limitation is the relatively small number of trials. Only English or German language studies were included in this analysis. No Chinese databases were searched, and no Chinese or other language studies were included. This certainly contributes to the lack of larger trials and the small number of trials and may also have led to language bias. The subgroups of this analysis are therefore partly characterized by a small number of patients and partly by a small number of studies. The AA subgroup of this analysis consisted of only two trials with a total of 39 patients

actually treated with AA. The subgroups examining combined interventions were based on only one study each. In addition, there is considerable heterogeneity in both the pooled data set and the subgroup analyses. This may be, next to different control interventions, due to relatively small sample sizes, heterogeneous patient populations, differences in study methodology, and/or differences in the implementation of acupuncture interventions. Because of these considerations, the multiple regression model did not reach significance in our case and cannot be considered an appropriate statistical tool for this analysis.

4.3. Implications for Practice and Research

Despite some limitations, this analysis indicates that acupuncture may be an effective modality for pain relief in the treatment of cancer pain. Crucially, acupuncture showed significantly better results than the control modalities, suggesting specific effects. (57,115) To make a translation of these findings into clinical practice, it is useful to examine the clinical relevance of the results to the patient. A systematic analysis by Olsen et al. showed that the pooled average of the minimum clinically important difference (MCID) for pain relief was -1.6 points ([95% CI: -1.4 to -1.9]; I^2=91%), including cancer-related pain. As pain perception and thresholds vary, the MCID on NRS ranged from -1.0 to -2.3 points and the median was -1.5 points. (100) This indicates that a reduction of -1.4 to -1.9 points on the NRS is necessary to be clinically relevant and actually produce pain relief for the patient. As the results of this meta-analysis showed, acupuncture significantly reduced cancer pain by -1.50 points on the NRS (pooled MD [95% CI: -2.41 to 0.60], p<0,01). This indicates that the results of this meta-analysis are therefore within the MCID´s 95% CI and can be considered to be within the defined range of the pain relief that is clinically relevant. (100) This supports the clinical efficacy of acupuncture in the treatment of cancer pain, strengthens the scientific base, and may help to promote the integration of acupuncture into multimodal therapy. Given the prevalence of cancer and cancer-related pain in the general population, and the fact that a significant number of patients continue to suffer from cancer pain despite pharmacologic interventions, acupuncture

represents a valuable integrative approach to the management of this pain. (1,2,4) However, as mentioned at the beginning, every therapeutic treatment has a prescribed dose. The dosage of acupuncture is still an understudied area, making it difficult to expand the use of acupuncture. Determining the appropriate dose would be particularly important for clinical application, but clinical studies and research would also benefit and make new advances. Another factor that strongly influences the integration process is the socioeconomic context. To the best of our knowledge, this is the first meta-regression to examine the relationship between dosage and analgesic effect in cancer pain. As mentioned at the beginning, cancer patients are a vulnerable group facing physical, logistical and financial burdens. The results of this meta-regression show clear trends that a higher number of sessions, a longer duration in weeks and a higher intensity of treatments may lead to improved pain relief. In terms of clinical implementation, this would mean that clear logistical considerations would have to be taken into account. It would be necessary to offer concepts that allow increased intensity, duration, and number of therapies to cancer patients with limited physical and time resources. For patients, increased intensity would mean seeing an acupuncturist several times a week. In reality, this is hardly feasible. Therefore, the option of an inpatient setting would have to be offered, or a mobile team of acupuncturists would have to be available to make home visits several times a week. Concepts would also need to be developed to provide a greater number of treatments (measured in sessions or weeks), e.g. by offering sessions in combination with oncology appointments or other therapies. In this context, dosage is essential to determine what structures and framework conditions need to be created to ensure that patients with health and social problems receive a feasible and appropriate treatment plan and that this plan can actually be implemented. These are dose-dependent factors that influence cost-effectiveness and whether acupuncture is a value to the health care system. At this moment most health insurance companies do not cover acupuncture for cancer pain, which is an additional financial burden for patients who already have high medical costs. (122) Several studies have examined the factors that discourage patients from seeking treatment and have clearly shown

that financial burden and lack of insurance coverage play a major role. (123–125) A study by Schwehr et al. also showed that patients with insurance coverage for other indications were significantly more likely to receive the full course of treatment. (126) Liou et al. conducted an analysis of patients with cancer pain and found that about half of the respondents would use acupuncture if it were covered by insurance. (127) Currently, in Austria and Germany, treatment costs are only reimbursed on a case-by-case basis, which limits access to adequate treatment. (122,127–129). So there have been some studies that have looked at the cost-benefit ratio of acupuncture in pain management and found it to be a positive adjunctive therapy. (130–133) Therefore, in order to obtain more accurate results and to improve the financial barriers, it is necessary to evaluate the treatments from an economic point of view. To this end, it is particularly important to gain a deeper understanding of the dose-response relationship of acupuncture. So, to further promote the integration of acupuncture, there is an urgent need for more well-conducted clinical trials that investigate the efficacy and dosage of acupuncture for cancer pain. As an impetus for necessary changes, the limitations of the present work should be considered. A previously mentioned problem that leads to imprecise results and difficulties in interpretation is the imprecision of protocols, especially with regard to the interventions. In some cases, there are no precise protocols and acupuncturists deviate from the planned interventions, or there is a lack of documentation of many factors. (68,115) Improving documentation is one way to optimize and improve the validity of effect sizes. The Consolidated Standards of Reporting Trials (CONSORT) checklist and the Nonpharmacologic Treatment Extension checklist were developed to improve reporting in RCTs. (134,135) They have been expanded to include the 2010 updated Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) checklist, an official extension of CONSORT, for acupuncture trials. (136) It is recommended that all three checklists be used for accurate reporting. In this context, the new STRICTA checklist places particular emphasis on more precise recording of the implementation of acupuncture interventions, but also of control interventions. It consists of six items that are

further subdivided into 17 details for more precise guidance. A brief overview of the content is given in Table 6.

Item	Detail
1. Acupuncture rationale	Acupuncture style (e.g. TCM, Japanese, Western medical) (a) including reasoning of use and references (b) and the use and extent of variation and individualisation (c)
2. Details of needling	Number of needle insertions per patient per session including mean and range (a), naming points or locations (b), the depth of insertion (c), required and actually elicited responses (f.e. De Qi, muscle twitch) (d), needle stimulation including manual techniques or details of electrical stimulation (e), retention time of the needle (f) and various information on the needles used (g)
3. Treatment regimen	Number of sessions including number of weeks (a) and freguency and duration of sessions (b) with variations of each documented with range and mean
4. Other components of treatment	Other interventions that only the acupuncture group received, such as cupping, exercises, lifestyle advice or similar with details (a) and context provided to the patients, such as information on diagnosis and setting
5. Practitioner background	Information on acupuncturists, such as qualification and years of practice including median and range (a)
6. Control or comparator interventions	Rationale for the use of control including reference (a) and detailed information on control interventions also using Items 1 to 3 of the checklist (b)

Table 6: Brief Overview of the Revised STRICTA Checklist (136). Six items and summaries of the details

The aim of the checklists and detailed reporting is to increase transparency, reduce ambiguity, and provide information necessary for the reproducibility of studies. Improving the quality of protocols facilitates the interpretation of results and increases the accuracy of results, which could significantly advance research. (136) More precise reporting would also be beneficial for clinical implementation, as effective interventions from trials and studies could be accurately translated into practice. Chen et al. conducted an analysis using linear regression to examine the influence of the STRICTA checklist factors on analgesic effect. In summary, many factors played a role, but frequency and duration of sessions were the most important. (68) Consistent with the results of this meta-regression, dosage plays a

critical role and should at least be well documented. Because the mechanisms of action of acupuncture are not fully understood, further multivariable analyses including other characteristics of acupuncture should be conducted and more information on the reference ranges of certain parameters should be provided. (68,110) The most robust way to obtain more precise results on dosage would be to compare different treatment regimens in controlled trials that have strict consistency of protocols and the greatest possible congruency of characteristics besides dosage. (68) The trials used in this analysis generally had detailed protocols, including characteristics of interventions and controls. However, further efforts in this direction could lead to better reproducibility between RCTs, which could provide greater homogeneity and thus improve the results. The further development of acupuncture research has already provided a scientific basis for the traditional experiential knowledge of TCM and thus enabled the beginning of its integration into Western medicine. Further methodologically stringent and uniformly conducted research, as well as reliable reporting and evaluation of results, could accelerate progress and help achieve further recognition as an integrative measure to improve cancer pain therapy.

In closing, I would like to express that the remaining uncertainties and limitations should not discourage practitioners from continuing their own efforts. After all, TCM therapies have been in practice for thousands of years, and one's own empiricism should not be disregarded, especially in the individualized care of patients.

Identification of AI tools

The following tool was used to optimize the language of the text:

Tool: DeepL Pro and DeepL Write Pro

Provider: DeepL SE

Date of content generation: 18.09.24-23.09.24, 10.-12.10.24, 8.12.24-18.12.24, 21.01.-14.04.25

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