

# Emerging medical applications based on non-ionizing electromagnetic fields from 0 Hz to 10 THz

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**Abstract:** The potential for using non-ionizing electromagnetic fields (EMF; at frequencies from 0 Hz up to the THz range) for medical purposes has been of interest since many decades. A number of established and familiar methods are in use all over the world. This review, however, provides an overview of applications that already play some clinical role or are in earlier stages of development. The covered methods include modalities used for bone healing, cancer treatment, neurological conditions, and diathermy. In addition, certain other potential clinical areas are touched upon. Most of the reviewed technologies deal with therapy, whereas just a few diagnostic approaches are mentioned. None of the discussed methods are having such a strong impact in their field of use that they would be expected to replace conventional methods. Partly this is due to a knowledge base that lacks mechanistic explanations for EMF effects at low-intensity levels, which often are used in the applications. Thus, the possible optimal use of EMF approaches is restricted. Other reasons for the limited impact include a scarcity of well-performed randomized clinical trials that convincingly show the efficacy of the methods and that standardized user protocols are mostly lacking. Presently, it seems that some EMF-based methods can have a niche role in treatment and diagnostics of certain conditions, mostly as a complement to or in combination with other, more established, methods. Further development and a stronger impact of these technologies need a better understanding of the interaction mechanisms between EMF and biological systems at lower intensity levels. The importance of the different physical parameters of the EMF exposure needs also further investigations.

**Keywords:** pulsed electromagnetic fields, low frequency electromagnetic fields, high frequency electromagnetic fields, millimeter waves, THz waves, bone healing, cancer treatment, neurological treatment, diathermy

## Introduction

A number of medical applications for both diagnosis and therapy rely on different parts of the non-ionizing part of the electromagnetic (EM) spectrum. Non-ionizing radiation refers to electromagnetic fields with frequencies from 0 Hz (static fields) up to 3.0 PHz. Such a wide frequency band includes ultraviolet and visible light, infrared radiation, millimeter waves, radiofrequency fields, low-frequency electromagnetic fields, and static electric and magnetic fields. Although medical applications are found among all these frequencies, this review deals specifically with the frequency range from 0 Hz to 10 THz (see [Table 1](#) for a summary of relevant frequencies and their nomenclature).

Some of the applications that originate in this part of the frequency spectrum are well established, have been used since decades, and are based on mechanisms of action that

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**Table 1** Terminology and frequency ranges of the parts of the non-ionizing EMF spectrum that is covered in this review

Classification	Sub-class/division	Abbreviation	Frequency
Static fields	Static electric fields Static magnetic fields	SEF SMF	0 Hz
Low frequencies	Extremely low frequency electric or magnetic fields Intermediate frequency electromagnetic fields	ELF EF ELF MF IF EMF	1–<300 Hz 300 Hz–<100 kHz
High frequencies	Radiofrequency electromagnetic fields (“radiowaves”) Microwaves Millimeter waves Terahertz waves	RF EMF MW MMW THz	100 kHz–<300 MHz 300 MHz–<30 GHz 30 GHz–<300 GHz 300 GHz–10/30 THz

are well understood. An example of such an application is magnetic resonance imaging (MRI). This diagnostic tool employs three different kinds of magnetic fields (static magnetic fields, gradient magnetic fields in the kHz range, and radiofrequency electromagnetic fields) for its function. This technology lies at one end of the spectrum both regarding use and penetration, and also regarding market size. It seems that the annual global market is reaching billions of US\$ (see, e.g., [www.marketsandmarkets.com](http://www.marketsandmarkets.com), accessed 4 Jan 2019). At the other extreme lies such applications as the use of small permanent magnets for pain relief, a therapeutic modality which is considered “fringe” medicine, with no or weak clinical evidence and lacking understanding of any putative mechanism.

There are also a number of applications, which are serving as complement to more established diagnostic or therapeutic tools that are based on different kinds of electromagnetic fields (EMF). Some of these applications are relatively well known and established, such as electrosurgery, and diathermy as a treatment modality, e.g., muscle pain. Other applications have a certain niche and seem to be increasingly accepted and then also used in the clinical setting, such as stimulation of “nervus vagus” to treat epilepsy. Still others are in clinical use but have a weaker evidence base when it comes to randomized clinical trials (examples include hyperthermia treatment by radiofrequency EMF as tumor treatment, pulsed EMF for bone fracture healing). Still other applications are presently at the research stage and although receiving interest within the scientific community, lacking proper clinical investigations. In many of the cases where a therapeutic effect is strived for, the underlying mechanism of action is poorly or not at all understood.

The exposure to the EMFs in the frequency range of interest should not cause damaging effects to either the

patient (unless they are outweighed by the beneficial effects), the operator, or, any third party. To assure safe exposures, exposure guidelines have been developed and are regularly revised based on the available scientific knowledge. The most influential exposure guidelines are published by the International Commission on Non-Ionising Radiation Protection (ICNIRP) and serve as guidelines for the responsible national competent authorities. Such guidelines exist for several frequency bands, including low frequency electric and magnetic fields,<sup>1</sup> high-frequency EMFs,<sup>2</sup> and for diagnostic devices.<sup>3</sup>

## Purpose

The purpose of this article is to summarize and assess the available knowledge regarding EMF-based therapeutic tools that are in various stages of development. Certain novel developments in diagnostics will also be shortly mentioned. However, widely established modalities such as, e.g., MRI and electrosurgery are not covered by this review. The technologies that are presented do not represent all the approaches that are available. Instead, a number of techniques that are possibly becoming more main-stream are described. They are used for different clinical areas (which is the primary level of structuring the very diverse material) such as bone healing, cancer treatment, neurological applications, diathermy, and other applications. The specific EMF-based modality (technology) is then discussed in the context of the clinical situation. Some examples that are provided present approaches that are at earlier stages in the value chain, basically being subjected to research and early stage clinical studies.

## Bone healing

Nonunion and/or delayed union fractions constitute a large fraction (10%) of the almost eight million annual fracture

patients in the United States.<sup>4</sup> These slow-healing fractures are more common among the elderly, patients with diabetes, obese patients, and smokers.<sup>5</sup>

EMFs, especially pulsed EMFs (PEMFs), are investigated since decades regarding a possible role in bone fracture repair. One of the first studies by Basset<sup>6</sup> in this area suggested that PEMFs induced forces through piezoelectricity leading to bone repair/formation. This and subsequent studies employed a biphasic low-frequency signal, as a non-invasive method.<sup>7–9</sup> The US Food and Drug Administration (FDA) approved this signal for the application for non-union/delayed fractures in 1979, particularly for fractures that are not regenerating with conventional medical treatment.

The mechanisms of action are unclear although many studies have provided at least some useful knowledge. Thus, further studies from Basset's group showed that the field application influenced cellular calcium efflux and influx.<sup>8</sup> According to Markov,<sup>10,11</sup> the effects were caused by the induced electric fields rather than by the magnetic component of the fields since electric currents can depolarize cells by triggering ion fluxes over the membrane. Also, studies by Pilla propose that the primary agent is the PEMF which induces electric fields<sup>12</sup> which then trigger  $\text{Ca}^{2+}$ -Calmodulin dependent signal transduction pathways.<sup>13</sup> Panagopoulos et al<sup>14</sup> have suggested that the initiation of changes in ion fluxes is due to that EMF triggers vibration of ions on the cell membrane surface. These vibrations would in turn regulate the openness of voltage-gated ion channels. Other groups proposed that the magnetic fields (MF) are inducing certain observed effects by penetrating to the inside of the cells and there reorienting, e.g., membrane proteins. This would then affect ion or ligand binding and ultimately the cellular biochemistry.<sup>15</sup> Presently, it is thought that PEMF devices induce electric fields with a magnitude from 1 mV/cm to 100 mV/cm. This stimulates bone cells in the same way as mechanical stress, leading to enhanced growth and remodeling effects.<sup>16</sup>

A number of cellular effects that may have relevance for the bone-healing properties of PEMF have been published. *In vitro* studies have demonstrated PEMF effects on hormonal signaling, such as inhibition of parathyroid hormone and osteoclast activating factor,<sup>17</sup> but also stimulatory effects on endothelial cell proliferation and capillary formation.<sup>18</sup> PEMF increases osteoblast activity but significantly reduces osteoclast formation<sup>19</sup> and increases differentiation of pre-committed mesenchymal stem cells into bone tissue<sup>20</sup> Zhai et al showed on osteoblast-like MC3T3-E1 cells treated with 15.38 Hz PEMF (0.5, 1, 2, or 6 hrs/day) at various intensities (magnetic flux densities

of 0.5 mT, 1 mT, or 2 mT; 3 consecutive days) that the fields induced osteoblastic behavior by means of a Wnt/beta-catenin pathway.<sup>21</sup> Furthermore, the field exposure has been shown to regulate downstream osteogenesis-associated gene/protein expressions. PEMF stimulation at 2 mT, 2 hrs/day, had the strongest stimulating effect on osteoblast proliferation. Furthermore, cell-protective effects were detected via the activation of the PI3K/Akt/Bad signaling pathway (for overviews see<sup>22,23</sup>).

Angiogenesis is a part of a successful bone fracture healing. Appropriately, it was demonstrated that PEMF exposure (1.5 mT, 75 Hz) positively influences the release of anti-inflammatory cytokines and angiogenic factors as well as increase tendon cell proliferation and tendon-specific marker expression in a human tendon cell culture model<sup>24</sup> PEMF has been seen to complement angiogenesis since it causes the endothelium to release FGF-2<sup>25</sup> There is a large bulk of literature available demonstrating PEMF effects in cellular models (for a recent review see<sup>26</sup>), where effects on osteogenesis and chondrogenesis occur due to gene expression changes, increased bone matrix deposition, and stimulated cellular proliferation and differentiation. The authors point out that PEMF application has different effects, which are depending on at what time during the repair process that exposure takes place.

*In vivo* studies have been performed, e.g., on rabbits (25 mT, 0.1–4 Hz),<sup>27</sup> dogs (0.1–2.4 mT, 15 Hz),<sup>28</sup> and also on rats (0.2–0.2 mT; between 15 Hz and 63 kHz)<sup>29–32</sup> showing a statistically significant improved bone repair, even though that Atalay et al<sup>32</sup> detected no statistical differences between control and stimulated bones at day 30. However, there are a number of problems when animal studies are extrapolated to clinical settings because of species differences, making data interpretation useful for the clinical situation problematic.

Several clinical studies have investigated the PEMF effects on patients, with different results (e.g.,<sup>9,33–41</sup>). The main problem with such studies seems to be that they are too small, not well organized, and thus inadequate to provide evidence regarding the clinical efficacy of the PEMF exposure paradigm. However, Hannemann et al<sup>42</sup> did not see any difference between PEMF and control when they analyzed data from 13 studies of nonunion healing. Regarding the time to radiological union, they found significant bone growth stimulation effects of PEMF treatment specifically in fractures that were not treated with surgery and on upper limb fractures. Accelerated radiographic union was also seen among

patients subjected to hind foot arthrodesis when exposed to PEMF<sup>43</sup> Assiotis et al<sup>40</sup> investigated how efficient PEMF is in treatment of both delayed unions and nonunions of the tibia and found that longer treatment duration was correlated with successful unions.

It was recently shown in a double-blind randomized study that time to complete union as seen on X-ray in fifth metatarsal fractures was shortened (14.7 weeks in controls compared to 8.9 weeks among PEMF treated subjects). A number of molecular markers typical for osteogenesis were seen at increased expression levels after treatment with PEMFs.<sup>44</sup>

## Cancer treatment

Although EMFs in medicine are used since long for therapeutic or diagnostic purposes, the use in cancer treatment is basically an emerging concept, of interest especially if conventional treatment options are limited. This is the case of, e.g., untreatable brain tumors, because certain high-molecular weight and/or hydrophilic anti-cancer drugs cannot penetrate the blood–brain barrier or if all other therapeutic options (radiotherapy, chemotherapy, targeted antibodies, or other pharmacological treatments) cannot eliminate the malignant growth. There are different concepts<sup>45</sup> (discussed in more detail below) using different frequencies of the EMF spectrum with or without signal modulation, to treat specific tumors, with electric (TFields, electroporation) or EMFs (hyperthermia, RF treatment), or in combination with chemotherapeutics or nanoparticles (see also Table 2).

## Hyperthermia/radiofrequency ablation (RFA)

Hyperthermia refers to heat treatment to kill cancer cells by temperature increase (40–45°C)<sup>46</sup> and is used concomitant with radiation therapy or chemotherapy.<sup>47,48</sup> The rationale is that hyperthermia makes cancer cells more sensitive to radiation and may furthermore improve the effects of cytostatic drugs. The efficacy regarding tumor size reduction has been investigated in clinical trials,<sup>49</sup> which have investigated treatments of tumors such as sarcoma,<sup>50</sup> melanoma,<sup>51</sup> lung cancer,<sup>52</sup> breast cancer,<sup>53</sup> cervix cancer,<sup>54</sup> and head and neck tumors<sup>55</sup> (for a review about the mechanisms see<sup>56</sup>).

The hyperthermia treatment can be local, regional, or involve the whole body, depending on the tumor's size and location.

Local hyperthermia is used to heat a small area (max. 5 cm across) with very high temperatures to eliminate cancer cells and adjacent blood vessels. The heat may be applied to the surface of the body, inside body cavities, or deep in tissue through the use of needles or probes. Radiowaves, microwaves, ultrasound waves, and other forms of energy can be used for heating. Thus, RFA of small tumors is a relatively common type of local hyperthermia. RFA uses high-energy radiowaves (MHz frequencies) for treatment with a needle-like probe that is inserted into the tumor during surgical procedure for 10–30 mins under radiological control (ultrasound, MRI, or CT scans). RFA is mainly used to treat liver cancer,<sup>57</sup> but its use to treat kidneys,<sup>58</sup> and lungs<sup>59</sup> is under investigation. Long-term outcomes after RFA treatment is not yet known, but there are some ongoing phase III investigations. As recently shown, e.g., in Japan, RFA is widely used for liver cancer treatment; therefore, its application for other cancer types is available.<sup>53</sup> A phase I study with localized early breast tumors (maximum diameter of 2 cm) showed a 90% complete ablation rate, and an ongoing phase II multicenter study evaluates the long-term safety and efficacy of RFA as well as its potential to reduce or avoid mastectomy.<sup>53</sup>

Regional hyperthermia, the heating of only a part of a body, is usually combined with chemotherapy or radiation therapy in order to weaken cancer cells so that they will be more easily killed by conventional methods ([www.cancer.gov](http://www.cancer.gov)). For deep tissue treatment, similar devices are used as in local hyperthermia treatment.<sup>46,49,50,60</sup> Another approach for certain cancers such as melanoma, liver or lung cancer, which may be difficult to treat since they are large tumors and/or dispersed, is to remove the blood of a patient, heat it and supply it with relevant pharmaceuticals and then perfuse the patient. This can be done for regional perfusion or for continuous hyperthermia peritoneal perfusion.

Whole body heating is suggested to improve chemotherapy in the treatment of metastatic cancers by rising the body temperature using heating blankets, warm-water immersion, or thermal chambers ([www.cancer.gov](http://www.cancer.gov)). It is thought that whole body heating activates certain immune cells and induce they cell-killing capacity.

Protocols depicting Standard Operating Procedures (SOPs) are available which are necessary to obtain replicability between different clinical trials.<sup>61</sup> Furthermore, prior to the hyperthermia sessions, simulations that take power absorption and/or temperature patterns in the patient into account are generally performed.<sup>46</sup>

**Table 2** EMF tumor treatment methods used in clinical oncology or at the research stage

Technology /modality	Physical characteristics	Action mechanism	Condition for treatment	Clinical studies <sup>a</sup>
Hyperthermia/ radiofrequency ablation (RFA)	Invasive treatment during surgical procedure using a needle or a RF-EMF probe.	Tumor necrosis via thermal ablation	Mainly used for the treatment of liver metastases.	+
Nanoparticles assisted radio frequency ablation (NP-RFA)	Non-invasive loading of tumors with nanoparticles, which are externally exposed to RF-EMF. The generated heat inducing an inside-out hyperthermia.	Tumor necrosis via thermal ablation by improved efficacy of thermal damage.	NP-RFA in combination with radiotherapy for treatment of recurring glioblastoma and recurring breast cancer.	–
Tumor treating fields (TTFields)	Invasive application of electrodes to the skin, 200 kHz electric fields, for 18 hrs daily.	Mitotic spindle disruption, anti-proliferative effect of cancer cells. Molecular mechanism is unknown.	Treatment of glioblastoma following tumor resection and radiation therapy.	–
Tumor specific frequency modulated RF-frequency	Non-invasive treatment by a spoon-shaped antenna in the mouth; 27.12 MHz carrier frequency modulated with cancer specific frequencies of 1873.5 Hz, 2221.3 Hz, 6350.3 Hz, and 10,456.4 Hz; SAR <2 W/kg; whole body exposure for 3 hrs/day.	Mitotic spindle disruption, anti-proliferative effect of cancer cells. Molecular mechanism is unknown.	Treatment of advanced hepatocarcinoma and its metastases.	–
Electroporation (EP)	Electric fields; 300–400 mV for <1 ms in vitro; train of eight EPs of 100 $\mu$ s; invasive 1000 V/cm; non-invasive 1300 V/cm.	Induction of tumor/cell death by the formation of aqueous pores in the lipid bilayer.	Treatment of solid tumors.	+

**Note:** <sup>a</sup>Presence (+) or absence (-) of randomized clinical trials.

## Nanoparticles-assisted RFA (NP-RFA)

RFA treatment would be improved by a method which is non-invasive. For that, the RF probe is replaced with heat mediators such as nanoparticles (NP), which are heated up by an externally applied RF-EMF, so that tissues will be heat-treated in a non-invasive way.

Superparamagnetic iron oxide nanoparticles (SPIONs) and iron oxide nanoparticles (IONPs) are examples of nanoparticles that are candidates for RF-cancer treatment. There are also other nanomaterials made, e.g., from gold, iron oxide, cobalt, or carbon-based, and also quantum dots that seem to exhibit strong heating responsiveness to RF in *in vitro* experiments (for an overview see<sup>62</sup>).

The RF heating is caused by Joule heating or magnetic heating.<sup>63</sup> So far, there are no optimal conditions for effective RF-heating of NPs. The degree of heat generation is given by the specific absorption rate (SAR), which in turn is affected by several factors (magnetic field amplitude and frequency; the nanoparticles' material, size, shape, crystallinity, concentration, aggregation; and environment viscosity).<sup>63</sup> Aggregated (in contrast to dispersed) particles influence the tissue distribution of the particles, as well as exhibit different heating characteristics. Furthermore, large particles respond to external fields faster and will thus heat up quicker and will also be quickly cleared by the blood circulation. Therefore, the candidate NPs need a specific size that responds to the physical conditions in an optimal way. For instance, SPIONs need to be small (less than 150 nm) to ultra-small (less than 50 nm), for an optimal magnetic response.<sup>64</sup> The electromagnetic radiation used in magnetic hyperthermia is in the range from several kHz up to 1 MHz.<sup>65</sup>

Radiotherapy together with magnetic hyperthermia has been tried as treatment of recurring glioblastoma multiforme and recurring breast cancer.<sup>66,67</sup> The results were promising in the sense that radiation doses could be lowered in the combined treatment compared to radiation treatment alone and that side effects were reported to be modest. Furthermore, studies have shown that the magnetic hyperthermia stimulates cancer cells' oxygenation, which leads to increased radiosensitivity.<sup>63</sup> This is especially important in situations where traditional radiotherapy is insufficient due to exceptionally high radioresistance, which is the case with melanoma cells.

Besides the numerous *in vitro* and *in vivo* studies, also a few clinical trials have been performed.<sup>66</sup> However, the limited efficacy observed in these trials

slows down the implementation in the clinics. In Germany and the Netherlands, magnetic hyperthermia is already included in the assortment of treatments for several types of cancer diseases. Clinical trials are ongoing to treat pancreatic, prostate, and esophageal tumors.

## Tumor Treating Fields (TTFields)

TTFields therapy is a novel non-invasive treatment modality based on electric fields. The FDA approved the method in 2015 for the use in patients with the astrocytoma tumor glioblastoma multiforme (GBM) and in combination with the chemotherapeutic drug temozolomide (TMZ) for the treatment of newly diagnosed GBM. GBM is fairly common (15% of all primary brain tumors and 46% of the primary malignant brain tumors<sup>68</sup>) and highly aggressive with poor prognosis. Patient survival remains low, 25% at 2 years, and 5% at 5 years.<sup>69</sup>

TTFields are target-cell type dependent, where the applied frequency is specific for the specific type of tumor cells. The fields are working at low intensity, disrupt specific structures during mitosis, and subsequently induce apoptosis. TTFields change the polarity of tumor cells at the intermediate frequency range (100–300 kHz). The frequency used for glioma treatment is 200 kHz.<sup>70</sup> *In vitro* studies have shown that cellular growth is negatively affected by electric field strengths of about 1 V/cm or higher and that maximal growth inhibition is reached by 2.5 V/cm.<sup>70</sup> The sensitivity to TTFields is especially high in cells that divide fast. Since TTFields decrease the ratio between polymerized and total tubulin and have effects on polar macromolecules and organelles, they counteract the build-up of the mitotic spindle. Subsequently, what follows is aberrant mitosis which in turn leads to chromosomal damages and caspase-dependent apoptosis of the daughter cells.<sup>71</sup>

Another hypothesis regarding the TTFields effect suggests that the changed cellular morphology during cytokinesis cause intracellular electric fields that are particularly strong at the cleavage furrow. The inhomogeneous fields generate dielectrophoretic forces that may cause aggregation of charged structures, and thus disrupting mitosis (see also<sup>72</sup>). Tuszynski et al<sup>73</sup> analyzed the two explanation models presented above from a quantitative biophysical perspective. They concluded that both ionic condensation waves around microtubules and dielectrophoretic effects on the dipole moments of microtubules are plausible mechanistic candidates.

Numerous preclinical studies provided support for that TTFields could be a therapeutic option for malignancy. Consequently, clinical trials have been performed and even guidelines for clinical settings have been published (for overviews see<sup>69,74,75</sup>). More recently, the phase 3 EF-14 international clinical trial showed that combined treatment of newly diagnosed GBM patients with TTFields and temozolomide increased overall survival with 5 months compared to patients treated only with temozolomide. Patients also reported an improved quality of life and fewer side effects.<sup>76</sup> Accordingly, the FDA has recently approved the combination of TTFields and temozolomide for the treatment of newly diagnosed GBM.<sup>75,77</sup>

TTFields therapy is a physical and thus a non-chemical mode of action-based therapy, which has no “half-life”. The antimitotic activity stops as soon as the TTFields therapy ends. Consequently, there is a need for continuous application of the fields. It has been shown the most efficient TTFields treatment duration exceeds 18 hrs per day.<sup>78</sup> The required application of the transducer arrays directly to the shaved scalp and the need to have the power supply for the TTFields-unit present at all times can be quite inconvenient for patients. However, novel versions of the device that are lighter than the original one are expected in the near future. Furthermore, ongoing trials that study the effect of TTFields on low-grade gliomas and on other cancers (solid tumor brain metastases, non-small cell lung cancer, and pancreas cancer) are underway.

## Electroporation (EP)

EP is a technique to increase the permeability of the cell membrane in order to deliver drugs or genes into a tumor cell. This is done by exposing cells and tissues to electric pulses with high amplitude and short duration. This causes aqueous pores to be formed within the membrane, which in turn causes membrane permeability to increase.<sup>79</sup> Mir et al.<sup>80</sup> were the first who combined pulsed electric fields at high voltages with bleomycin (used for chemotherapy) into a novel clinical application, electrochemotherapy (ECT). The first gene transfer into mouse fibroblast clonal cell line (lyoma cells) by EP was performed by Neumann et al.<sup>81</sup>

ECT is a way to locally treat solid tumors without tissue heating and ablation. The principle behind its applications is the opening of the cell membrane for a short time caused by a few short and intense electric pulses. Administration of cytotoxic drugs (or genes) takes place during this permeabilization, whereby a relatively high local dose with enhanced cytotoxic effect can be reached.

Since the permeabilization is lasting for a short time, the cell membrane “heals” fast which promotes cell survival.<sup>82</sup>

There are several theoretical considerations of the events underlying the phenomenon; however, the present view is that electroporation forms aqueous pores in the cell membrane.<sup>79</sup> The actual mechanism behind the pore formation itself is however unknown. The pore formation occurs very fast, within nano- to microseconds, whereas their resealing needs seconds to minutes.<sup>83,84</sup>

According to Calvet and Mir<sup>82</sup> there are three different applications of EP that are in clinical use: 1) Electroporation to transfer drugs and small molecules without major side effects, as a local treatment without distinct effects on distant metastases (usually trains of eight 100- $\mu$ s pulses); 2) electro-gene-therapy, also called gene electrotransfer, which transfers nucleic acids to the inside of the cells without using viruses; the electroporation is often longer (tens of milliseconds) and combines short and long pulses. There are also specific electric pulses for cellular uptake of naked plasmid DNA<sup>79</sup> 3) the irreversible electroporation (IRE) which uses short high-voltage electric pulses to induce cell death through permanent membrane lysis or loss of homeostasis. Although the local ablative effect and that the tumor cell killing is not selective induce side effects on normal cells in the tissue, this application has been approved for clinical use in the US by the FDA.<sup>85,86</sup>

The specific number and duration of EP pulses for a tissue/cell depend on the local electric field distribution. Typical settings are 300–400 mV across the membrane for <1 ms. Reversible pore formation is achieved if fields are below 800 V/cm.<sup>87</sup> Different EP protocols are applied depending on the applications and the tumor's biological and physical parameters.

The release of European Standard Operating Procedures of ECT (ESOPE)<sup>88</sup> in 2006 was the starting point for a routine use of ECT. The document states complete tumor regression was seen in 73.7% of the treated nodules with an overall response of 84.8%, 6 months after one single ECT session. A train of eight EPs lasting 100  $\mu$ s and of appropriate field amplitude has to be delivered using either invasive (EPs of 1000 V/cm) or non-invasive electrodes (EPs of 1300 V/cm), depending on the depth and the size of the nodules.<sup>82,88</sup>

By 2019, around 150 cancer centers in Europe are applying ECT for treatment of metastases and primary tumors ([www.nice.org.uk](http://www.nice.org.uk)), showing positive patient-reported outcomes in large multicenter investigations.<sup>89</sup> Comparisons with other palliative treatments is difficult due to lack of appropriate studies. However, the complete response rate is

in the range of 30–65%, and a 1-year disease control between 30% and 90%, depending on tumor type.<sup>89</sup>

ECT treatment furthermore causes an immunological response. The treatment leads to immunogenic cell death which has a vaccine-like effect triggering a cytotoxic immune response against remaining cancer cells (e.g.,<sup>90</sup>). Case studies and retrospective investigations have shown the combination of ECT with immunotherapy can lead to regression of nodules that have not been treated by ECT. This suggests that a systemic antitumor response may occur, which has prompted calls for clinical trials which compare ECT treatment only with treatments comprising ECT plus immunotherapy.<sup>91</sup>

A variant of EP uses calcium instead of the anti-cancer drugs bleomycin or cisplatin, inducing cell death via necrosis due to the large quantities of intracellular calcium. There are *in vitro* and *in vivo* studies showing the anti-tumor effectiveness of such “calcium EP”<sup>92</sup> The first randomized phase-II study included 7 patients with a total of 47 cutaneous metastases from breast cancer and malignant melanoma<sup>93</sup> The patients were subjected to either Ca<sup>2+</sup> (0.5–1 mL/cm<sup>3</sup> of tumor volume) or bleomycin, before EP treatment. The calcium-EP treatment reached almost the same response rate as treatment with ECT together with bleomycin (72% and 84%, respectively), although causing lower rates of wounds (38% vs 68%). Six months after treatment, recurrence was seen in 2/18 and 3/19 tumors, respectively. A relapse 1 year after treatment was found in 3 metastases out of 25.

In summary, ECT combines high-voltage electric pulses with an anti-cancer drug. The method seems to be safe and effective for local treatment of cutaneous and subcutaneous melanoma metastases. ECT seems to be useful also for patients with inoperable tumors that are in pre-irradiated areas and for tumors that are not responding to chemotherapy.

Further advances of EP are related to new combination strategies, such as the combination of ECT with immunotherapy. The potential for clinical use of calcium EP is further investigated, as well as gene electro-transfer and radiotherapy. The development of new instrumentation with favorable tolerability profile that can treat deep-seated malignancies (primary pancreatic carcinoma, bone, liver, and brain metastases) is ongoing. Furthermore, there are also clinical trials investigating EP suitability for such tumors.

## Tumor-specific RF frequencies

Previous insomnia<sup>94</sup> studies prompted Barbault et al<sup>95</sup> to suggest that modulated RF-EMF at certain frequencies

affect proliferation of human tumors, which was subsequently investigated. The effects of a number of modulation frequencies were studied on several parameters (“biofeedback”, including electrical resistance of the skin, heart rate, blood pressure) in patients with different cancers. Those patients that suffered from a specific type of malignancy exhibited biofeedback responses to the same frequencies<sup>95</sup> The authors exposed 163 patients with a cancer diagnosis, to a carrier frequency of 27.12 MHz RF-EMF (which is globally approved for medical use) and identified a total of 1524 modulation frequencies ranging from 0.1 Hz to 114 kHz that the biofeedback technique responded to. Most frequencies (57–92%) were specific for a single tumor type. Only four modulation frequencies (1873.5 Hz, 2221.3 Hz, 6350.3 Hz, and 10,456.4 Hz) were found to overlap in multiple tumor types, specifically breast cancer, hepatocellular carcinoma (HCC), prostate cancer, and pancreatic cancer.<sup>95</sup>

Costa et al<sup>96</sup> performed a single-group, open-label, phase I/II study where they investigated how safe and effective it is to expose patients inside the mouth to very low levels (SAR <2 W/kg) of EMF. The authors used frequencies specific for HCC in patients (n=41) with poor prognosis in a protocol that employed 1 hr treatments three times per day. One-third of the patients (34.1%) did not show any tumor progression even beyond 6 months. Times for median progression-free and overall survival were 4.4 (95% CI 2.1–5.3) and 6.7 months (95% CI 3.0–10.2), respectively. One almost complete response and three partial ones were recorded. A clinical study began in 2012 (<https://clinicaltrials.gov/ct2/show/NCT01686412>) where healthy control subjects and patients (chronic hepatitis B, HCC, breast cancer) are exposed to random modulation frequencies or to frequencies specific for HCC or breast cancer. This study reportedly ended in September 2015, but no further information is available.

Although potentially interesting, only few publications are available regarding this modality. The publications are furthermore from a single research group and no independent replication study has been published. Further studies are needed to determine if there is an impact of amplitude-modulated RF-EMFs on cancer treatment.

## Neurological applications

Recent decades have seen an increasing interest in the use of different EMF-based technologies for the treatment of pathologic conditions related to the nervous system. A few of these EMF approaches are well established and part of



the common treatment arsenal, such as transcutaneous electric nerve stimulation (TENS; pain treatment)<sup>97,98</sup> and electroconvulsive treatment (“electroshock”) of certain psychiatric conditions.<sup>99</sup> These technologies will not be further discussed in this review. This section will overview some technologies that have substantial amounts of clinical data available, which makes it possible to make an evaluation of the appropriateness of the respective technologies. Techniques that are in early stages of development are not discussed due to the sparse available database.

The basic concepts of the different approaches can be divided into a) electrical stimulation that directly triggers nerve activity, b) magnetic field treatment that is causing induced electric fields which are strong enough to cause neuron depolarization, and c) weaker (E)MF that potentially act as facilitating agents, lowering the threshold for probability of induction of nerve cell depolarization’s.

## EMF modalities used in the treatment of neurological conditions

Some examples of these technologies are shortly described in Table 3 and include vagal nerve stimulation (VNS), (repetitive) transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), transcranial pulsed EMF (PEMF), and low-frequency sine wave magnetic fields (LF MF). These modalities are used to treat different conditions, which are discussed in the following sections.

The brain stimulation technologies can be invasive or non-invasive (see<sup>100,101</sup> for useful reviews). Invasive techniques use implanted electrodes either directly into the specific regions of the brain (DBS) or connected to afferent branches of the tenth cranial nerve, as in VNS. Non-invasive stimulation on the other hand relies on devices placed on the external surface of the skull.

VNS stimulation devices can either be surgically placed subcutaneously (“invasive”) or be kept outside of the body (“non-invasive”), which allows for the patient to perform adjustments of stimulation characteristics as acutely needed. The invasive variant was the first developed and remains the most commonly used with over 100,000 recipients suffering from epilepsy.<sup>102</sup> The device was approved for treatment of refractory epilepsy by FDA in 1997, and later also approved for treatment of major depression disorder (MDD) in 2005.<sup>103</sup> The stimulator is placed subcutaneously in the upper chest wall, and its electrodes are passing under the skin to the left cervical

branch of the vagus nerve. Typically, the stimulator is activated 2 weeks after surgery. Besides these two diseases, studies have been performed to see if the approach can be used for the treatment of other conditions, inter alia pain conditions, stroke, and as an anti-inflammatory device.<sup>103–105</sup>

According to Chen et al,<sup>106</sup> DBS began in 1987 as treatment modality for Parkinson's disease (PD) and is presently replacing approaches that ablate parts of the brain in order to treat essential tremor, PD, and primary dystonia. The method, which is FDA approved for PD treatment, is employing electrodes placed in a specific, and for the disease condition appropriate, nucleus of the brain. The electrical currents are delivered by a neurostimulatory device placed under the skin in the thorax region. The electric pulses have frequencies up to a couple of hundred Hertz, at a few V in voltage.

The first study describing a non-invasive way to stimulate the motor cortex was published by Barker et al.<sup>36</sup> An external coil was placed on the scalp, delivering a PEMF. The non-invasive approach evolved to what is today rTMS, which is using sinusoidal or static MF. The specific targets for the treatment can be obtained by placing the coils in a way which affects a specific part of the cerebral cortex<sup>107</sup> causing a direct stimulation of neural elements or acting more distally via modulation of the activity in connecting networks. The repetitive nature of the stimulation in rTMS may also confer effects on synaptic plasticity and neuronal viability,<sup>107</sup> as well as having an epigenetic component.<sup>108</sup>

Conventional approaches to treat a multitude of disease conditions are established and having mostly high rates of success. However, there are also plenty of cases where established pharmacological interventions are only partly successful, and also possibly causing side effects that are so grave that the therapeutic value is questionable. There is in such cases that novel methods, not only based on EMF approaches of course, are sought after with special interest. Here we address some conditions related to the health of the nervous system where technologies based on EMF have received interest, and where there are studies addressing not only proof of concept but also the efficiency of the treatment modalities. This includes treatment of chronic pain, therapy-resistant depression, and epilepsy. There are also studies addressing nerve regeneration, migraine, and other types of headache, and neurodegenerative disorders, which will be mentioned in this section.

**Table 3** Overview of emerging EMF-based technologies for treatment of pathological conditions associated with the nervous system

Technology/modality	Physical characteristics	Action mechanism	Condition for treatment	Clinical studies <sup>a</sup>
Vagal nerve stimulation (VNS)	Invasive (implanted neurostimulator) or non-invasive (external stimulator) delivery of electric pulses to left afferent nervus vagus. Pulse frequencies 20–30 Hz, durations <500 $\mu$ s, 0.25–3.0 mA, given as on-off cycles (e.g., 30–90 s on, 5 mins off).	Incomplete knowledge about how VNS modulate the CNS. Additionally, it has been suggested that VNS activates the cholinergic anti-inflammatory pathway, which could affect both CNS and peripheral organs.	FDA approved for treatment of refractory epilepsy and major depression disorder. Also used for treatment of chronic pain, migraine. Some studies of treatment of other conditions.	+
Repetitive transcranial magnetic stimulation (rTMS)	Static or time-varying MF delivered by external coils to selected regions of the brain. Low ( $\leq 1$ Hz) of high-frequency (>5 Hz) pulses, at B-field strength strong enough to cause E-fields capable of neuronal firing. Treatment provided during single or multiple sessions (each lasting tens of minutes).	Low frequencies cause decrease in neuronal excitability, high frequencies increase cortical excitability. Long-term effects on neurotransmitter actions and synaptic plasticity.	Treatment of resistant depression (FDA approved). A number of other conditions have been treated in occasional studies.	+
Deep brain stimulation (DBS)	Electrical currents delivered by electrodes in various nuclei of the brain. Up to hundreds of Hz, 10s–100s $\mu$ s long pulses; weak currents (mA).	Unclear.	FDA approved for treatment of essential tremor, Parkinson's disease, and obsessive compulsive disorder. Tested also for epilepsy, depression and a number of other psychiatric disorders.	+
Transcranial pulsed electromagnetic field (tPEMF)	Externally located coils (e.g., helmet contained) deliver MF (50 Hz, mT levels, square wave pulses, similar to bone healing PEMF) to skull, inducing E-fields in brain tissue (0.1–4.0 mV/cm).	Induced E-fields far below neuronal firing level. Suggested mechanisms include activation of receptor tyrosine kinase signal transduction pathway, and graded depolarization of membrane potentials.	Therapy resistant depression.	+
Low frequency magnetic field (LF MF)	Sine wave MF delivered either continuously or as pulses. $\leq 300$ Hz, typically 50 Hz. Flux densities (sub) mT levels for different periods of time.	Unclear mechanism, although both effects on neural transmission and on neurotrophic action has been proposed.	Nerve regeneration in spinal cord injuries	–

**Note:** <sup>a</sup>Presence (+) or absence (-) of randomized clinical studies.

Most of the treatment modalities are supposed to mediate their action by brain stimulation, either on a superficial tissue level or penetrating into deeper parts of the brain. Still other methods are based on application of electric or magnetic fields to specific nerves or to the spinal cord.

## Epilepsy

Several reviews have been published on the subject of treating epilepsy with VNS. A recent paper<sup>102</sup> stressed that VNS is the first choice in the treatment of epilepsy forms not susceptible to common pharmaceutical treatment. The VNS approach seems to be useful for various types of seizures, with few and mild side effects. A more specialized review was published by Fisher et al.<sup>109</sup> They analyzed studies where patients had the possibility to manually activate (“on demand”) the VNS stimulator (as opposed to devices that function without the patient's active participation). Twenty studies were included, including 859 subjects. On average, 45% of the patients responded favorably to the treatment in these studies, and 28% experienced seizure cessation. This review also included five pre-clinical studies, where patients were getting induced seizures in the lab. VNS treatment immediately before or after onset of seizures caused attenuation or even cessation of attacks.

## Depression

VNS has also received FDA approval in 2005 for treatment of otherwise treatment-resistant depression in adults.<sup>103</sup> Several reviews have summarized clinical studies and found evidence for beneficial effects. Thus, Cimpianu et al<sup>105</sup> performed a systematic review of 25 studies, which mostly were single-blind, open-labeled observational or cohort studies. Most of the studies provided evidence for the efficacy of this treatment modality. Another meta-study found support for efficiency of VNS when used as an add-on therapy to anti-depressive pharmacotherapy,<sup>110</sup> in line with an evaluation by<sup>104</sup> However, it seems that multicenter randomized clinical trials are still not available.

Other modalities that have received interest as agents for depression treatment include DBS and transcranial PEMF. The former was used in a study on epilepsy patients (n=25) with depression. Stimulation in the right frontal cortex (100 Hz; 100  $\mu$ s pulse width; 1 or 6 mA; 100–200 s duration) caused a dose-dependent mood-state improvement lasting several days as evaluated by a validated questionnaire and electrocorticography.<sup>111</sup>

The use of transcranial PEMF has its roots in the bone healing studies using PEMF, employing similar fields with low flux densities that are unlikely to initiate action potentials.<sup>112</sup> In this approach, one or several coils are placed over the head and stimulating large areas or even the entire cerebral cortex. Anti-depressant effects have been studied both in preclinical and clinical studies, as overviewed by<sup>112</sup> Examples of specific studies include the work by Martiny et al<sup>113</sup> who performed a sham-controlled double-blind study on 50 patients. The patients were treated or sham-treated for with square-formed pulses (50 Hz; 3 ms on and 12 ms off) with a B-value of 1.9 mT measured 0.5 cm from the coils. The authors concluded that this would generate induced E-fields around 30  $\mu$ V/cm ten cm from the coils, far below the voltages that are necessary to cause action potentials. Treated patients clinically and statistically significantly improved by the five weeks treatment, seen within the first weeks. A 50 Hz PEMF (0.1–4 mV/cm) was used in another double-blind study.<sup>114</sup> Patients were kept on anti-depressant medication at baseline levels throughout the study, which compared one or two treatments per day. The patients exhibited a high degree of remission in both cases (around 70% in both groups after 8 weeks). Five weeks treatment yielded around 30% remission in both groups, so the authors concluded that the treatment period rather than the dose (exposures/day) was important. The effect sizes in these two studies are higher than with conventional anti-depressant treatment according to the authors.

A two-year follow-up study on 49 of the original 65 patients<sup>115</sup> showed that 48% had experienced relapses during the years after the first treatment. Of these patients, 55% responded to a second treatment with clear remission, 18% with partial remission, whereas 27% did not respond. The research group also treated depression patients with apathy sub-syndrome for 8 weeks. These patients responded with remission in 66.7% of the cases if treated twice per day. One treatment per day was inefficient.<sup>116</sup>

Another approach in depression treatment is based on rTMS, which is an FDA-approved method since 2008 for the treatment of adults that have not responded to prior anti-depressant medication. In contrast to the other methods mentioned here, rTMS employs stronger magnetic fields generated by coils placed on the skull. The flux densities are high enough to cause induced E-fields of such a magnitude that they depolarize neurons.<sup>117</sup> Dependent on the type of coils which is used, the MF can project to either more superficial or deeper regions

of the brain. Both types are used for the treatment of major depression disorders, which is the main application area for TMS,<sup>117</sup> although also treatments of other conditions are being studied. A systematic review of the evidence for safety and efficacy of this treatment was published by Perera et al.<sup>118</sup> Studies were assessed and graded according to criteria set by University of Oxford's Centre for Evidence-Based Medicine. The treatment protocols mostly used included daily left prefrontal TMS exposure over 4 to 6 weeks (comprising 20–30 sessions), with frequencies at 10–18 Hz, and peak B-field up to 1.5 T. Three multisite randomized controlled trials were identified, providing consistent conclusions that supported effective treatment. This was also supported by a number of large, multisite observational studies. However, the efficiency would be even better if the right patients were selected for treatment.<sup>119</sup> The author argues that different predictors of response are possible, but that they have not been sufficiently investigated. Such factors can be related to the patient, different aspects of the disease, and the TMS procedure itself.

## Pain

EMF-based modalities have also been tried to treat various kinds of pain. There seems to be two different kinds of biological mechanisms that are addressed, including features that are part of inflammation processes as well as neural transmission (see<sup>120</sup> and references therein). The different devices include TENS, which employ two or more electrodes that are connected to the skin and deliver electric currents to afferent cutaneous nerve fibers. These stimulations are given at frequencies above 50 Hz or below 10 Hz and cause  $\mu$ -opioid and  $\delta$ -opioid receptor activation, respectively.

Transcranial direct current stimulation (tDCS) has been employed for migraine treatment, whereas solenoid coils and Helmholtz coils, that generate PEMF, have mostly been used for downregulation of pro-inflammatory molecules that are involved in pain. Krath et al<sup>121</sup> performed a prospective randomized clinical trial (RCT) on patients with lower back pain, who either received conventional therapy or such therapy combined with PEMF during 6 weeks (totaling eight sessions). Both the self-diagnosed pain and the degree of disability decreased in both groups although statistically significantly more ( $P < 0.001$ ) in the combined treatment group. This particular study employed a very short (ns) pulse released at 3 Hz, at 80–150 mT. The positive effect remained after 12 weeks post treatment. Successful PEMF treatment of fibromyalgia has been reported,<sup>122</sup> although the clinical relevance of the

treatment was questioned by the authors. Positive effects on osteoarthritis (OA)<sup>123</sup> have also been shown. This latter study made a meta-analysis of published OA studies and found that knee pain, but not cervical pain, was improved by treatments, but also pointed out that employed PEMF protocols were heterogeneous and no “standard” protocol has been established. A case in point is a recent study that reported lowering of subjective arthritis symptoms and lowered blood pressure and heart rate variability.<sup>124</sup> The study was small, five patients of which four were positively affected by the treatment. The subjects were treated with a PEMF from a commercial applicator (20–60 mins, 2 to 3 times per week for 4 weeks). The study reported that different frequencies of the PEMF were used, and information about magnetic flux density is missing. No negative controls were used. Such a study is thus difficult to evaluate.

A PEMF based on a 27.12 MHz RF field was shown in another study<sup>123</sup> to be successful in patients with post-operative lumbar pain (double-blind multicenter RCT), if pulses were of a certain pulse width (42  $\mu$ s), but not shorter.

At least regarding the effects of LF PEMF on inflammation-related pain, a possible mechanism has been suggested by Vincenzi et al,<sup>125</sup> who showed that PEMF treatment causes upregulation of the anti-inflammatory adenosine receptors A<sub>2A</sub> and A<sub>3</sub>, which in turn cause decreased levels of PGE<sub>2</sub>, IL-6, and IL-8, as well as an inhibition of NF- $\kappa$ B transcription. This could possibly be relevant for, e.g., osteoarthritis treatment. Recently, it was also shown that LF PEMF (75 Hz; 1.5 mT; 24-hr exposure) reduces inflammation in LPS-activated N9 microglia cells via signal pathways that involve JNK1/2.<sup>126</sup> The exposure was reducing ROS production in the cells and decreased the cells invasive and phagocytic properties.

rTMS has also received some interest in the treatment of chronic pain associated with spinal cord injury. However, the numbers of available clinical studies are small and the studies furthermore have different parameters for stimulation and clinical characteristics.<sup>127</sup> Analgesic effects have been reported also for use of VNS in both human and animal studies of spinal cord injury,<sup>127</sup> as well as in treatment of primary headache disorders.<sup>127</sup> There are also studies reporting effects of PEMF on pain. One example is a randomized double-blind sham-controlled study focused on 56 female patients suffering from fibromyalgia,<sup>128</sup> which reported significant improvement in several subjective pain scores. The whole-

body exposure was to a 40  $\mu\text{T}$  MF, 0.1–64 Hz, 30 mins twice per day for 3 weeks.

## Nerve regeneration

Still another topic that has received some preliminary interest, although clinical studies are mostly lacking, is nerve regeneration. Several studies have used the crushed sciatic nerve in the rat as model and studied both functional, morphological, and biochemical endpoints. Thus, improved regeneration was observed after LF MF exposure to sine waves at flux densities up to 0.5 mT.<sup>129–131</sup> A variation on this thematic was done by using a rotating magnetic field which delivered variable flux densities to the animals depending on the positioning of the exposure coils.<sup>132</sup> Several flux densities, all at 40 Hz, were used in the study, and the highest interval (150–300  $\mu\text{T}$ ) provided the largest improvement to regeneration compared to sham-control conditions. Improved regeneration of both nerve and muscle in mice subjected to crush injury of the upper thigh (PEMF at 10 or 50 Hz),<sup>133</sup> as well as positive effects on hemi-sectioned spinal cord in rats (50 Hz sine wave; 17.96  $\mu\text{T}$ )<sup>134</sup> have also been reported. None of these studies was performed in a blinded manner, and the dosimetry information is in some cases insufficient.

A recent review considering PEMF effects on spinal cord regeneration was covering *in vitro* as well as *in vivo* studies and the few clinical studies that are available.<sup>135</sup> The authors concluded that any regenerative effect was dependent on that the signal used first reduced inflammation, which then allowed regeneration *per se* to proceed. Such positive effects have been reported with PEMF at frequencies below 100 Hz and flux densities that are at or below 5 mT.

## Dementia

The possibility to use brain stimulation as a treatment for dementia type disorders have been suggested, although very few studies have investigated this subject. Chang et al<sup>136</sup> reviewed this topic and concluded that the available pilot studies for Alzheimer's disease (AD) treatment provide mixed findings. Furthermore, the studies are very diverse and do not follow any standardized study design with larger sample sizes and longitudinal follow-up. Nevertheless, the authors suggested that rTMS warrants further studies based on available findings.

A different approach for the treatment of AD has been developed by Arendash<sup>137</sup> Available data are from transgenic mice overexpressing a mutant form of the human

APP gene, rendering the animals prone to cognitive impairment, and excessive extracellular build-up of amyloid-B (A-B plaques). The treatment device employs a 918 MHz radiofrequency signal, providing a specific absorption rate (SAR)-value of 1.05 W/kg to the animals. The treated animals exhibited better results in behavioral tests, reduction of extracellular AB-plaques, and less intracellular aggregation of AB than the unexposed transgenic animals. The paper referred to a planned pilot clinical study, but no results from such a one have been published so far.

## Diathermy

Tissue heating induced by high-frequency EMF has also a decades-long tradition as a tool in physiotherapy, going by the name of "diathermy". Available applicators operate in two different frequency areas. So-called shortwave (SW) diathermy uses primarily 27.12 MHz as continuous or pulsed waves to obtain deep tissue heating in addition to superficial heating, which is mostly localized to the skin and the subcutis<sup>138</sup> (FDA 2015 recently reclassified the term SW diathermy to non-thermal short wave therapy, at 13.56 or 27.12 MHz.) The SWs are coupled to patients by a capacitor or inductor, whereas the other form of diathermy (microwave, MW, diathermy) provides radiation beamed from the applicator.<sup>139</sup> In contrast to SW diathermy, MW diathermy employs higher frequencies, 2.45 GHz or sometimes 915 MHz (in the USA).

Diathermy treatments aim to cause a regional increase in blood flow, which can be obtained if tissue temperatures are above 41.5°C.<sup>140</sup> The tissue responses to these kinds of treatments are thus possible to explain with known mechanisms for thermal interactions.<sup>141</sup> Increased blood flow in turn would increase nutrient and O<sub>2</sub> availability, improve tissue elasticity, normalize tissue pH, and also have analgesic effects.<sup>140</sup> The latter would have their origin both in the changed metabolic conditions and in direct neurobiological effects.

The possibility to use diathermy as pain-relieving agents is commonly used in physiotherapy, and several clinical studies have addressed the efficacy of such treatments for a number of conditions. The study results are mixed, both positive effects and no effects have been seen. For example, in a study on chronic neck pain,<sup>142</sup> patients (n=149) in a double-blind RCT were treated with physiotherapy exercises and TENS in addition to real or sham MW diathermy at an output power of 80 W. There were no observed differences between groups. Another study investigated MW diathermy effects on chronic

lower back pain in patients undergoing exercise treatment. The patients that were treated with MW as well ( $n=19$ ; 20 min per day, 3 days per week for 6 weeks; 100 W) did not experience any beneficial effects from the MW treatment.<sup>143</sup>

In contrast, several studies have found support for the beneficial effects of SW diathermy. Wang et al<sup>144</sup> made a systematic review and meta-analysis of the treatment of patients with knee OA. The authors identified eight RCTs that compared SW with sham or no intervention. The outcomes showed a pain-relieving effect, and increase in leg extensor muscle strength, but no significant effect on physical function of the leg in treated patients. The effects were more pronounced during pulsed exposures in contrast to continuous exposure. Similarly, beneficial effects (statistically significant, but small) on pain and muscle performance have also been found.<sup>145</sup> However, the effects were only noted in the patients that experienced a local thermal sensation, which indicates that placebo was playing a role for the results. Takahashi et al<sup>146</sup> compared SW and MW diathermy in combination with injection of hyaluronic acid into the knee of OA patients. Eight patients were treated once per week (3 weeks) with a 100 W, 10-min MW protocol, without any positive effects. Nine other patients underwent SW treatment (8 MHz; 200 W; 20 mins) for a similar time period. These patients reported additional improvements compared to the injection only treatment.

The efficacy of deep heating MW therapy on OA patients was shown by<sup>147</sup> The comparison was made between MW treatment (3x30 min per week for 4 weeks; 434 MHz; 40 W) and superficial heating caused by application of “hot packs” (sessions comparable to MW). The arthritic conditions improved in the MW-treated patients, and remained at a 12-month follow-up investigation, whereas the superficial heating had no effect.

Other examples of positive therapeutic effects of diathermy concern tendinopathy-related pain<sup>148</sup> (434 MHz; three RCTs), chronic pelvic inflammatory disease<sup>148</sup> (one double-blind RCT; SW diathermy), and idiopathic carpal tunnel syndrome<sup>148</sup> (27.21 MHz; 15 sessions á 15 mins).

There seems to be more beneficial effects noted in studies using SW diathermy than MW diathermy, although both modalities show a mixture of results. One mechanistic difference may be at hand though, illustrated by a recent study on blood flow in the lower limbs of female subjects ( $n=40$ )<sup>148</sup> Both SW (27.12, 240 W) and MW diathermy (2.45 GHz; 200 W) caused sustained skin heating after treatment (albeit longer lasting by SW). However,

Doppler measurements of blood flow noted increased blood flow only during SW treatment.

Despite that diathermy has a long tradition in physiotherapy as primarily a pain-relieving modality, the efficacy has not been strongly substantiated in double-blind multicenter RCTs. Number of patients are low in several studies, and blinding is questionable in many of the publications. The actual dosimetry is seldom considered, which likely will differ substantially between patients with different tissue compositions, even if the output power from the diathermy device is at a standard setting.

## Other applications

There are a number of other conditions where research has investigated the potential for EMF, either alone or in combination with other modalities, to function as a therapeutic agent. Furthermore, certain properties of high-frequency EMF have also been investigated for their usefulness in diagnosis.

## Wound healing

One area where there are both basic and clinical studies available is within the general area of wound healing. The overall picture seems to be that a possible potential for wound healing exists in certain patient groups, possibly combined with pharmaceutical treatments.<sup>149</sup> Positive clinical results have been obtained with both PEMF and ELF MF. The picture is more mixed when specific types of wounds are investigated. Recent Cochrane reviews of PEMF (27.12 MHz) therapy for pressure ulcers<sup>150</sup> and for venous leg ulcers<sup>151</sup> point to that: 1) useful RCTs for structured reviews and meta-analyses are very few, and often having methodological problems, and 2) that results in individual studies are inconsistent. Thus, parameters like healing rate and wound size reduction were seen to be both unaffected and improved by the PEMF treatment. Equivocal results have also been published regarding burn wound repair in Wistar rats treated with a 500 Hz MF at unknown intensity,<sup>152</sup> in rats with dorsal wounds treated with RF pulsed PEMF (up to 0.1 mT flux density, evaluated as tensile strength changes),<sup>153</sup> and in clinical studies of diabetic foot ulcers with electrostimulation.<sup>154</sup>

An interesting study regarding AC electric fields positive influence on wound healing was recently published.<sup>155</sup> The study has several innovative and novel aspects, both technically and related to modes of action. The authors inflicted wounds on the back of rats and monitored macroscopic and microscopic healing as well as molecular

markers during the healing process. Wounds that were treated with an AC electric field completed healing after 3 days, whereas the sham-treated wounds (on the same animals) needed on average 12 days for the healing. The electric field was generated by the rats' own muscle activity (breathing) and was by means of a “nano-generator” applied to the edges of the wound. The field was having an irregular frequency and amplitude related to the activity of the rat. Thus, active rats could generate asymmetrical, bipolar pulses up to 110 times per minute, with peak voltages up to 2.2 V. Accompanying mechanistic studies *in vitro* on NIH 3T3 fibroblasts suggested that the effects were mediated by facilitating fibroblast migration, proliferation, and transdifferentiation. In control experiments, a conventional generator of an AC electric field with constant frequency and amplitude also had effects on fibroblasts, but not such that healing parameters were stimulated. Instead, this treatment caused strong ROS production (up to 489% above control), whereas the nano-generator signal had modest stimulatory effect on ROS production, 65% above control.

### Immune system modulation

Several of the possible therapeutic effects of both ELF MF and PEMF could be due to that field exposure has a modulating effect on the immune system, leading to that pro-inflammatory cytokines and pathways are downregulated. This has been the thematic in a number of papers and is extensively discussed in Rosado et al.<sup>149</sup> A key role would then be played by tissue macrophages, which have shown to respond to both these kinds of fields with moderate oxidative stress and modest increases in ROS, as well as enhanced phagocytic activity (reviewed by<sup>156</sup>). The latter authors pointed out that immune system modulation could be a target for the treatment of certain inflammatory diseases, including some neurodegenerative diseases that have an autoimmune background.

An area where PEMF has been used for decades in clinical settings is the treatment of OA, primarily the inflammatory component and subsequent pain. However, despite a long clinical use, the evidence from available clinical studies is not conclusive. The treatment is often to low frequency asymmetric rectangular pulses<sup>157</sup> that can have different outcomes dependent on frequency, and at flux densities of 0.5–1.5 mT.<sup>158</sup> The data from laboratory studies consistently show that exposure of cartilage explants, chondrocytes, or both, to these fields have a positive effect on OA progression. The clinical outcomes

have on the other hand produced variable results.<sup>159</sup> More studies show positive outcomes than not, but positive outcomes are not consistently present. A more unequivocal clinical interpretation is needing more careful and well-designed sham-controlled prospective studies, with sufficient numbers of subjects.<sup>159</sup>

### Millimeter waves

The use of millimeter waves (MMW) for therapeutic application has a long tradition in the former Soviet Union, where physicians used these waves to decrease pain conditions, such as headaches and joint pain.<sup>160</sup> MMW are used alone or in combination with other modalities<sup>161,162</sup> as an alternative therapeutic modality for conditions such as dermatitis, cardiovascular diseases, diabetes, gastrointestinal disorders, pain relief, and wound healing. Certain MMW frequencies are preferred (42.2, 53.6, and 61.2 GHz) at power densities of 10 mW/cm<sup>2</sup> and less, which are too low to cause heating of the skin.<sup>163</sup> Treatments are typically lasting 15–30 mins every day for 5–15 days.

Internal diseases are treated at a number of anatomic or acupuncture points such as the lower end of the sternum. There the water-rich skin allows MMWs to penetrate a few tenths of millimeters.<sup>164–166</sup> The precise mechanism which then allows systemic effects is not known, but stimulation of the nervous system<sup>167</sup> and modulation of the immune system<sup>163,168</sup> have been suggested.

Despite the large number of patients treated in Eastern Europe, Western physicians have not accepted this technique due to the lack of well-controlled, double-blind clinical trials, and the lack of an accepted mechanism explaining how a localized MMWs exposure on the skin can be therapeutic for generalized pathologies. Both human and animal studies using “blinded” experimental conditions<sup>169,170</sup> have nevertheless brought about some evidence for general pain-relieving effects.

MMW have not found any established role as a diagnostic tool. One attempt to use the possibility to detect different water content in skin samples typical for psoriasis, eczema, malignancy, and thermal burn wounds is one of a few exceptions.<sup>171</sup>

### THz waves

THz radiation ranges in frequency from 300 GHz (the high-frequency end of the MMW band) up to 10 or even 30 THz (the edge of the far-infrared light band). The penetration depth of THz is typically less than that of microwaves, but it can penetrate non-conducting materials. Water absorbs

THz waves efficiently, thus allowing penetration in tissues to tenths of millimeters.<sup>172</sup> THz has received interest since it can be used for making imaging possible in locations not accessible to relevant investigations with conventional techniques, and with reasonable resolution. Suggested applications may include dermatological investigations to identify cancerous lesions, wound assessment, and even dental investigations.<sup>173</sup> A review of clinical trials investigating the usefulness of THz waves in cancer diagnostics has recently been published by Yu.<sup>174</sup>

Some skin conditions may be suitable for THz treatment,<sup>175</sup> but there is otherwise not much done regarding THz and therapy. The possibility for cancer treatment has been studied in a few investigations where non-thermal conditions are claimed to have been used (see<sup>176</sup> for a recent review). Some evidence suggests that THz radiation can affect the cells, their organelles, and the different macromolecules found within the cell (reviewed in<sup>177</sup>). Any effects of THz exposure can also be due to heating, caused by exposures to high-intensity continuous waves.<sup>178</sup>

Any possible therapeutic action of THz waves needs to be based on knowledge about biological effects of THz exposure. A key question here is if only thermal effects occur after THz exposure or if there is any possibility for non-thermal effects. The important distinction here is that thermal effects would affect the entire exposed tissue with all its cells. All effects would then be a consequence of increased temperature, which eliminates any “custom made” treatment of the tissue or the cells. In contrast, if non-thermal effects are possible, understanding their mode of action would allow for specific focus on certain processes or molecules. This issue was discussed in some detail in.<sup>179</sup> There may also be the potential for simultaneous use of conventional therapeutic modalities, such as pharmaceuticals, and THz waves.<sup>180</sup>

## MW breast imaging

The conclusive identification of a tumor is achieved by biopsy-based methods that use histology and biochemical and molecular markers to ascertain the status of a tissue. However, since this approach is invasive, costly, and requires highly skilled personnel, alternative strategies are employed. Among those, screening-based technologies are most commonly used. For breast cancer, the gold standard method is X-ray mammography, which nevertheless has certain drawbacks, including the use of ionizing radiation, and that it is less effective for detecting small tumors and in

dense breasts.<sup>181</sup> Accordingly, other methods are used to complement mammography.

MW imaging of breast tissue is a screening tool, which currently is in a development phase, and showing some promise. The imaging potential is based on that dielectric properties differ between tissues, which makes it possible to distinguish between normal and malignant tissue. The higher H<sub>2</sub>O content in tumors (due to increased vascularization and blood flow) is “seen” as changes in how MW energy is propagated, reflected, and attenuated in the tissue.<sup>182,183</sup> The result is that tumor tissue has higher values for dielectric properties, which can be monitored by wavelengths ranging from below 1 GHz up to a few GHz. Higher frequencies provide better resolution but allow less penetration depth, so imaging approaches often scan over a certain frequency range to obtain as much information as possible. Thus, a non-invasive and non-damaging tool is available since the output energy is low, leading to correspondingly low SAR-values in investigated tissues.

A number of clinical studies have been performed by different research groups,<sup>182,183</sup> where different scanning equipment’s covering a large frequency band (1–8 GHz) and their tumor detection rates have been compared with other available methods.<sup>183</sup> One recent investigation studied the tumor detection rate obtained when using a prototype ultra-wide band scanner that covered 3–8 GHz.<sup>184</sup> The study employed 86 patients recruited from a symptomatic breast care clinic and compared (blinded fashion) results obtained from mammography and ultrasound. The detection rate was comparable to mammography in fatty tissue (74% and 78% detection rate, respectively), and even better using MW imaging if breasts were having dense tissue. The prototype scanner has later been updated and the new model is currently used in larger multicenter clinical studies.

## Conclusion

Some of the applications based on various parts of the non-ionizing EMF spectrum that are covered in this review have at least some clinical impact, in the sense that they are more or less routinely used and accepted within the medical community. These include EP and ECT for treatment of certain cancer forms, rTMS for depression treatment, and possibly diathermy treatment for various pain conditions. What these approaches have in common is that the underlying mechanisms of action are more or less understood.



However, other application areas suffer from a lesser degree of acceptance, which at least in part is due to that therapeutic or diagnostic claims are based on weak evidence for an action mechanism at the used intensities of the fields. There is a large bulk of literature systematically reviewing the information regarding the underlying mechanisms between EMF and living matter (e.g.,<sup>10,11,26,185</sup>). However, the mode of action of EMF and cells is not clear at intensity levels that are not causing tissue heating (for high-frequency fields) or excitation of excitable tissues (for low-frequency fields). Also, there is an urgent need to systematically investigate which component of the fields (electric or magnetic fields) that affect cells and also which physical parameter is/are relevant for medical use (frequency, pulse form and duration, exposure time, field strength, etc.).

Even in the case of more established modalities, the technologies have not reached any major standing in the therapeutic field. This is due to both the mentioned lack of mechanistic understanding and also due to the scarcity of RCTs that have shown the efficacy and possible advantages with these technologies. The body of scientific literature provides many studies, both preclinical and clinical, but studies are often sub-optimally designed, and seemingly without consideration of previous experience provided by other scientists and clinicians. As long as study and user protocols are not better aligned, more coherent data and useful interpretations will be hard to obtain.

Strangely, many putative approaches that have shown some promise at the preclinical or early clinical stages seem to have disappeared from the research arena. This can be due to that results have not been able to replicate, and where the “negative” replication work is not published, but possibly also due to that funding is scarce and very competitive, and that funding bodies are not willing to invest in this kind of fairly “risky” research.

The pursuit of novel diagnostic and therapeutic medical applications is nevertheless needed, and it is likely that some EMF-based technologies will find at least a niche role, possibly as complement to and in combination with other established methods based on other physical principles, pharmacology, and novel biological approaches.

## Disclosure

The authors report no conflicts of interest in this work.

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