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Commentary

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Medical application of millimetre waves

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Introduction

The biological effects of millimetre waves (MWs) at power levels <20 mW/cm^2 were first discovered in the late 1960s, and within 10 years were studied in various countries including the former USSR,[1–4] Canada,[5,6] France[7] and Germany.[8,9] These early studies used a wide variety of objects ranging from biomolecules to bacteria to tissues of higher organisms. Poor reproducibility of some of the experimental results and the lack of acceptable theoretical models resulted in a significant delay to research activity in this area in the USA.[10–12]

In the meantime, based on the biological experiments, medical applications of MWs began in the former Soviet Union in the 1970s,[13,14] and since the mid–1980s, have been in widespread usage. Use of MWs for medical purposes is known as 'Millimetre Wave Therapy' (MW therapy), 'Extremely High Frequency (EHF) therapy', or, less frequently, 'Microwave Resonance Therapy'. With numerous medical MW generators now employed in hospitals and clinics in the former USSR and some other European states (some estimates range as high as 50 000 units[15]), thousands of patients undergo treatment with MWs every year. Some authors[16,17] claim that there are several hundred thousand patients who have been treated with MWs. The reported success rate of MW therapy for various pathologies is astonishingly high. However, this treatment modality is almost unknown to Western medical scientists and practitioners. There is only one publication on this subject in Western peer-reviewed medical journals.

We present an overview of the available information regarding MW therapy. The majority of information resides in Soviet/Russian/Ukrainian reports on this topic published as conference abstracts. However, their analysis allows us to reveal some general features of MW therapy. Upon comparing the clinical information with the existing experimental results, we can better understand the possible mechanisms involved, as well as the most potentially beneficial applications of MW therapy.

Physical characteristics of millimetre waves

MWs belong to a relatively narrow range of electromagnetic waves with wavelengths from 1 to 10 mm (corresponding to frequencies from 300 to 30 GHz, with 1 GHz $=10^9$ oscillations per second). MW generators and related equipment were produced primarily for military purposes (short-range radar), which, to a large extent, explains the secrecy and predominance of incomplete publications on this topic in the former USSR.

The penetration depth of MWs into biological tissues is very small. Unlike centimetre and decimetre waves, MWs are absorbed in water and water-containing media (including biological structures) within the first 0.3–0.5 mm from the surface, depending on the frequency used.[18–20] With energy insufficient to break chemical bonds directly,[21,22] and a low average incident power density of <20 mW/cm^2, MWs usually produce an average heating of an irradiated surface on the order of several tenths of a degree C, which is usually imperceptible.

Obviously the range of reported biological and

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medical effects of MWs cannot be explained by such a small bulk heating of structures. H. Fröhlich[21,23–25] suggested that such effects might occur through a resonance-type interaction, since some of the biomolecules and structural elements of the cells have their own theoretically calculated resonant frequency within the range of 10^{10}–10^{11} Hz. Several experiments showing narrow resonant frequency dependence of biological effects of MWs seem to support this hypothesis.[3,6–9,26,27]

However, other physical mechanisms may also be responsible for the biological effects of MWs. It has been shown, both theoretically[28] and experimentally,[29,30] that not only the absolute value, but the rate of heating is of critical importance for biological effects. The initial rate of heating due to MW exposure is usually very high, reaching 0.1–0.5 °C/s,[30–32] and is sufficient to produce some biological effects, such as an increase in neuronal firing rates.

Another important characteristic of MWs is their heterogeneous distribution on the surface of exposed objects. As shown by infrared thermography,[33] so-called 'localized hot spots' with a temperature elevation several degrees Celsius higher than the average can be formed on the surface of the skin.

Therapeutic potential of MW therapy

During the past 20 years, MW therapy has been used for a broad spectrum of diseases and conditions, some of which are listed in Table 1. The list of pathological conditions treated with MW therapy includes: some gastrointestinal diseases (peptic ulcer, gastroduodenitis);[34–39] diabetes;[41] coronary artery disease and some other blood circulation disorders;[42–45] cerebral palsy;[46] chronic non-specific pulmonary diseases;[47] skin diseases such as psoriasis and atopic dermatitis;[16,48,49] enhancement of bone and wound healing.[50–54] MW therapy has also been used to treat cancer patients, as a means of increasing their non-specific immunity and alleviating the toxic side effects of chemo- and radiotherapy.[55–57] There have been some promising results in the use of MW therapy for treating opioid, alcohol and nicotine dependencies.[16,58,59]

In all of the above cases, MW therapy seems to enhance regulatory effects, restoring a patient's homoeostasis.[17,39] This means that, depending on the condition of a patient, MW therapy can cause such changes as an increase or decrease of blood pressure,[45] stimulation of inhibited (or suppression of excessive) immune activity,[16,39,60,61] etc. For more data on efficacy of MW therapy in various diseases see Table 1.

Instead of sorting information according to disease, we will analyse it by the types of effect generated. Physicians using MW therapy, irrespective of the disease being treated, have observed some general features which form three main groups. They are: (i) sedative/analgesic effects; (ii) anti-inflammatory action and enhancement of tissue regeneration processes; and (iii) immune stimulation.

Sedative and analgesic effects

These are the most common effects of MW therapy which are cited by the majority of physicians and patients. Usually, after the first 2–3 sessions of MW therapy, 73–100% of patients report alleviation of, or even total relief from, the pain accompanying the disease, whether peptic ulcer,[34,36,62,63] heart disease[64,65] or a pruritic skin condition.[48,49] This is followed by normalization of sleep and improvement of general condition. Sleepiness sometimes develops during the MW therapy sessions.[65] Efficacy of MW therapy in treatment of males with psychogenic sexual dysfunction[66] can probably also be attributed to a general sedative action.

Pain relief is considered among the most general purposes of MW therapy application: in one of the largest cardiology centres in Russia, a clinical study is underway in which the decreased level of blood endorphins in patients with acute cardiac disorders is regarded as an indication for performing MW therapy.[67]

Some recent experiments confirmed that low-power MWs are capable of interacting with neurons affecting the electrical characteristics of neuronal functioning[27,30] and the production of some neuropeptides.[39] *In vitro*, MW directly affected such functions of neurons as firing rate, amplitude and form of the signal in marine skates,[68] frogs,[27,69] and snails.[30] *In vivo* exposure of mice to MWs increased by 40–50% the duration of anaesthesia caused by several non-opioid anesthetics.[70] The additional anaesthetic effect of MW was completely blocked by pre-treatment with the opioid antagonist naloxone, suggesting that MW therapy causes a release of opiate substances in the exposed organism. It is too early at this stage to make definite statements that opioids are being released in the body during MW therapy based on this one experiment, but some of the clinical data given below make such a possibility quite plausible.

A clinical study of 70 opioid drug abusers[58] revealed that MW therapy alone can significantly improve the conditions of patients suffering from withdrawal symptoms. After the first session of MW therapy, symptoms of abstinence were relieved for 2 h in 33.8% patients, up to 6 h in 50.7%, up to 12 h in 15.8%. Full relief usually developed after 3–12 sessions (days) of MW therapy. Drug abusers reported the sensory feelings comparable with those from

Table 1 Efficacy of MWT in treating various diseases

Pathology	Feature(s) studied	Patients treated	Efficacy	References
Malignant skin melanoma	Absence of metastases after surgery	59*	58.9% during 5-year follow-up versus 28.5% without MWT	(56)
Cancer of ear, nose and throat	Prevention of wound infection after surgery	50*	76% versus 35.3% without MWT	(56)
Atopic dermatitis	Prevention of relapses	112*	85% during 4-year follow-up versus 47% without MWT	(48)
Active lung tuberculosis	Cavities closing after 3 months of treatment	86*	59% versus 30% without MWT	78)
Peptic ulcer	1) Ulcer healing 2) Pain relief	2720*	1) 80.4% 2) 99.7%	(36)
Duodenal ulcer	1) Ulcer healing 2) Pain relief	20**	1) 95% in 2 weeks 2) 100% after 3–4 sessions	(96)
Peptic ulcer	Ulcer healing	148* and 50**	95%* in 17.2 ± 1.7 days 100%** in 11 ± 0.77 days	(62)
Peptic ulcer	Ulcer healing	50**	100% in 2 weeks	(54)
Unstable angina	Microcirculation, lipid peroxidation, immune activity	25* and 25**	Improvement of microcirculation, CD4+/CD8+ T-cells ratio normalization, SOD activity increased, serum complement activity decreased	(83)
Coronary artery disease	General conditions, in-hospital stay, blood tests	326*	Decreased duration of in-hospital stay, decreased stress reaction, improved blood counts	(64)
Acute heart attack	Pain relief	117**	Total pain relief in 97.3% patients	(98)
Hypertension	Cerebral blood flow	45*	Improvement of cerebral blood flow	(44)

* MWT was used together with an appropriate conventional drug therapy; ** MWT was used as a monotherapy.

drugs. About 60% of patients fell asleep during the MW therapy sessions. After the first session, the concentration of met-enkephalin in peripheral blood increased from 41 ± 8 to 252 ± 22 pg/ml, adaptogenic hormone prolactin from 7.0 ± 0.3 to 10.2 ± 0.3 ng/ml. Other researchers also seem to be optimistic about the therapeutic potential of MW therapy in treatment of opioid drug abuse, alcoholism, and tobacco smoking.[16,59] Experimentally-proven release of opioid substances in patients due to application of MW therapy would definitely substantiate such an optimism, as well as provide a basis for the wide use of MW therapy for any pathological condition where pain management is involved.

Anti-inflammatory and repair-stimulating action

Early experiments with wounded rabbits, mice and other laboratory animals[14,50–52,71,72] showed that the exposure of a wound surface to MW significantly enhances the rate of the recovery process by 1.5–2 times by decreasing the duration of oedema and exudative-inflammatory phases of wound healing. It has also been reported that MWs, when applied directly to an infected wound surface, can cause a sharp decrease in microbial contamination of the wound and favourable changes in the sensitivity of micro-organisms to some antibiotics.[51,52,71,72] The former can be a result of (i) the direct action of MWs on micro-organisms (*in vitro* inhibitory effects of MWs on various bacteria have been reported by several investigators[4,6,8,9]) and/or (ii) enhancement of the host's immune system. A decrease of R-plasmid-mediated resistance of *E. coli* to tetracycline has been observed *in vitro*,[51,73] and is potentially a very important feature of MW. It would be of special value when applying MW therapy for treatment of infected surface wounds (trauma, burn patients, etc.).

In clinics, MW therapy speeds up the recovery of patients suffering from various kinds of infected or clean wounds and fractured bones. The diseases where these characteristics of MW therapy are used range from gastric/duodenal ulcers to surface wounds (including such conditions as stasis ulcers of diabetic patients and infected burns) to complicated bone fractures, even with osteomyelitis.[53,56,74]

The only known double-blind clinical study of MW therapy in septic wound treatment was conducted by N. Korpan and colleagues at the Department of General Surgery, Kiev State Medical University.[75] This trial was a logical extension of Korpan's previous experiments on rabbits, in which continuous MW with a frequency of 37 GHz and incident power density of 1 mW/cm^2 applied directly to the wound area significantly accelerated healing of the surface wounds.[52,71] Two groups of patients with post-operative wounds (after surgery on bile ducts, gallbladder, pancreas, appendix, and after herniotomy) were included in this study: group A (71 patients) received standard wound treatment plus MW therapy; group B (70 patients) received, in addition to standard treatment, a placebo MW exposure from an ineffective generator. MW therapy was applied for 30 min daily for 7 consecutive days with the applicator of the generator placed 5–10 mm from the surface of the skin (wound area). Wound healing was significantly accelerated in group A: 5.6 ± 0.6 days vs. 10.2 ± 0.5 days for the placebo group. The time of initial epithelization, granulation, daily size of wound surface area and duration of in-hospital stay were significantly reduced ($p < 0.05$), by 1.8–2 times lower for the patients treated with MW therapy. The authors concluded that MW therapy was an effective method of post-operative treatment of purulent wounds after abdominal surgery. The above study could be viewed as the first published attempt to organize a clinical trial of MW therapy according to Western standards, and its results are encouraging.

In addition to treating the wound infections, MW therapy is reported to be an effective method of preventing post-surgical infections in cancer patients. According to Kabisov,[56] application of MW therapy in 50 nose, ear and throat cancer patients decreased the rate of infectious side-effects after surgery from 76% to 35.3%.

Interestingly, it has been observed that in most cases when peptic ulcer is treated with MW therapy, unlike any other known method, the ulcerous defect is healed without formation of scar tissue. This unique feature was first reported by the endoscopists who diagnosed peptic ulcer patients,[37,76] and confirmed by histological studies and electron microscopy. Biopsies from duodenal mucosa of 10 patients with duodenal ulcers treated with five sessions of MW therapy showed proliferation of poorly differentiated duodenal epithelial cells; normalization of the endothelial cell structure of microvessels (capillaries); and filling in the ulcer defect with a newly-formed granulation tissue. This granulation tissue contained fibroblasts, macrophages, mast cells and lymphocytes. Plasma cells with an augmented secretion of immunoglobulins prevailed. Samples obtained after 10 procedures of MW therapy showed complete epithelization of the former defect, frequently without formation of scar tissue.

The ability of MW to cause healing of skin without scarification was also demonstrated by dermatologists who treated skin wounds and lesions.[49,76,77] Based on this, several beauty clinics in Moscow and Kiev started using MW therapy in cosmetology.

Immune system stimulation

Laboratory investigations have confirmed that MW therapy produces non-specific enhancement of the human immune system. The changes include increased phagocytic activity of macrophages,[32,78] enhanced proliferation and normalization of the ratio of CD4+/CD8+ T-lymphocytes,[35,38,60,79] increased amount of B-lymphocytes and normalized production of immunoglobulins.[60,61,80]

Human peripheral blood macrophages appear to be very sensitive to MW therapy. For example, in a clinical study with active pulmonary tuberculosis patients,[78] MW therapy was used in combination with antibiotics. After 3 months of treatment, cavities in lungs resolved in 59% of patients from the MW therapy-treated group vs. 30% among the patients receiving antibiotics only. Numbers of macrophages in peripheral blood and their phagocytic activity (determined by the nitroblue tetrazolium [NBT] reduction test) were much higher in patients treated with MW therapy. In fact, the physicians used the NBT test as an indicator for the most effective frequency by exposing the blood samples *in vitro* to MW of various frequencies, and then choosing the frequency producing the highest increase in oxidative burst of macrophages. These data correlate with our findings that MW therapy can significantly increase the phagocytic activity of peritoneal macrophages against *Candida albicans* in mice treated with cyclophosphamide.[32] Here MW therapy caused enhanced antimicrobial immunity resulting in faster clearance of the affected organ/tissue from pathogens, as in several other experimental and clinical studies.[51,52,81,82]

Normalization of the CD4+/CD8+ ratio of T-cells was observed in blood of patients with cardiac,[83] diabetic,[17,84] oncological[16,57] and other pathologies. In response to MW therapy, T-lymphocyte function and numbers both improved.[32,48] Enhanced immune reaction mediated primarily through T-cells was found in mice exposed to MW.[85] The above combination of features, if confirmed, would make MW therapy a very powerful treatment modality.

Reported side-effects

Several clinical studies with hundreds of patients each[45,86–88] have reported only a few side-effects of MW therapy, and these were established without using a placebo control. Gunko and Kozshina[86] found that 3/528 patients (0.6%) with various internal diseases treated with MW therapy developed urticaria after 5–7 exposures. The pruritic rash in the abdominal and thoracic area disappeared after the end of the MW therapy course, and reappeared during the following repeated courses. Nevertheless, treatment of the patients with MW therapy was completed successfully. As the authors noted, urticaria developed only in the patients who during treatment had the radiator device in direct contact with skin in the area of the sternum. It is likely that urticaria was a result of mechanical irritation of skin or a localized allergic reaction, rather than of exposure to MW *per se*. This could have been easily checked by a sham exposure of sensitive patients, although the authors seem not to have done this.

In another study,[87] 6/326 peptic/duodenal ulcer patients (1.8%) receiving MW therapy, developed headaches and/or an increased blood pressure. The doctors switched these patients to a conventional drug therapy. According to Golovacheva,[88] who treated 415 patients with cardiovascular diseases, 5–26% of patients with hypertensive disease, heart rhythm disorders, and stable/unstable angina exposed to MW were 'hypersensitive' (the author's term) to MW therapy, which resulted in a $>5\%$ decrease of the initial blood pressure after the first 10 min of treatment. Nevertheless, using a special schedule of treatment (decreased duration of MW therapy procedures), the author successfully treated all her patients with MW therapy.

A transient increase of blood pressure by 20–30 mmHg during MW therapy sessions in a small portion of patients suffering from hypertension was also noticed by V. Kuzmenko,[45] although a decrease of this parameter by 15–20 mmHg occurred much more frequently. Other reported side-effects of MW therapy in this paper included temperature increases in subfebrile (body temperature 37–38 °C) patients, chest pain, and enhanced menstrual bleeding in women with abnormal menstrual cycles. Since no double-blind or simple sham exposure was used in the works cited, it is impossible to evaluate the role of such factors as mechanical irritation, psychological influence of the operator, placebo effects, etc.

The only known experimentally-observed potential risk of MW therapy is based on one published animal study,[89] in which rats were constantly exposed to MW at the power level 10 mW/cm^2 for a period of 58 days. As a result of this direct exposure, the eyes of rats became 33% less transparent to visible light—the animals had developed cataracts. Such experimental conditions are however very different from those used to treat patients: duration of exposure to MW was at least several thousand times higher, and no medical protocol includes direct exposure of eyes. Cataract formation was not found in other studies in which more clinically-oriented protocols were used. Furthermore, the very first publication on medical use of MW came from an ophthalmological clinic.[14] In this study, traumatic corneal wounds in the eyes of rabbits were healed by direct irradiation with MW. According to Cherkasov *et al.*,[14] who conducted these experiments, monitoring the animals for up to 1 year post exposure did not reveal any ophthalmologic abnormalities, including cataract development. Another experiment was performed recently by the team of H. Kues at John's Hopkins University.[90] They exposed the eyes of rabbits to MW with a frequency of 60 GHz at an incident power density of 10 mW/cm^2 for 8 h. No changes were observed by macroscopic tests or by post-exposure histopathological examination.

It may be useful to mention here a clinical report on the effects of MW therapy on the vision of patients with diabetes mellitus, which frequently causes retinopathy.[84] Exposure of the thymus and right shoulder areas of 20 patients (five with chronic recurrent uveitis and 15 with diabetic retinopathy in the pre-proliferative stage) improved the immune status of patients; their condition improved by 5–10 days faster than when conventional therapy was used. Electro-oculograms and electroretinograms improved significantly, as well as the vision of some patients.

Based on the above reports, it is reasonable to conclude that MW therapy, within the limits of frequency and power customarily used for medical purposes, is safe. However, it would be prudent to avoid unnecessary direct exposure to the eyes.

The MW therapy method

Essentially, MW therapy consists of exposure of certain areas of the skin to low intensity MW (for summary of MW therapy regimes see Table 2). Any one of several sites of application appears to be effective. Good results have been reported after irradiating various locations over the sternal area;[64,78] large joints such as the shoulder or hip;[83,91] some areas of the head such as the occipital area[44] or pineal gland projection area in the middle of the forehead;[56,57] biologically active zones and acupuncture points.[35,48,54] In any event, with the exception

Table 2 Typical regimens of MWT

Site of application	Wavelength (mm)	Frequency (GHz)	Power (mW/cm^2)	Duration of procedure (min)	Total sessions	References
Central area of forehead	7.1 5.6	42.25 53.57	~10	30 daily	10–15	(56)
Acupuncture points	5.6–4.3	54–70 tuned			10–15	(48)
Sternum (various locations over the sternal area)	7.1 6.4 5.6	42.25 46.88 53.57	10	40 CW or 60 pulsed daily	10	(78) (98)
Right shoulder joint area	7.1	42.25	10	30 daily	10	(83) (91)
Occipital area	7.1 6.4	42.25 46.88	10	30 daily	10	(44)
Wound area of surgical patients	8.1	37.00	1	30 daily	7	(75)

* CW, continuous-wave output.

of local treatment of skin diseases or open surface wounds,[48,49,75] the affected organ/tissue is usually remote from the site of application of MW.

The choice of frequency of MW is based on two alternative principles. According to the first one, backed by N. Devyatkov, M. Golant, and O. Betskii,[92] three 'therapeutic' wavelengths of 4.9, 5.6 and 7.1 mm (respective frequencies of 61.22, 53.57 and 42.25 GHz) were established as those that supposedly produce healing effects without harming the patient, and were approved by the Russian Ministry of Health. The second principle was introduced by S. Sitko *et al.*[93,94] This approach is based on tuning the frequency output of the MW generator, usually within 53–67 GHz range, according to the sensory response of a patient. A tuneable MW generator or a device which produced a wide-band noise signal with an extremely low power output was used. The site of exposure to MW preferred by these researchers is an acupuncture point or points.

Sensory feelings that some patients report in response to MW therapy are described as warmth, pressure, tranquillity, comfort, tingling, relaxation, light sleepiness.[58,65,75] The perception of low-power MW by humans seems to be supported by the results of a double-blind study in which objective electrophysiological parameters were recorded during exposure of volunteers; skin mechanoreceptors and/or nociceptors are suggested as the primary sensors,[95] although the mechanism(s) are still to be investigated.

A typical therapeutic session lasts for 15 to 30 min (sometimes up to 1 h), one exposure session per day, with a course comprised of 10 to 15 sessions depending on the nature and stage of a disease. In the course of treatment, the patient is positioned in the sitting or recumbent position. The exposure system, a metal horn or a dielectric radiator antenna matched with the generator waveguide, positioned over an irradiation site. The spacing between the waveguide and the patient's skin does not exceed 5 mm.[35,56,58,61,65]

Medical generators of MW

Initially, existing industrial millimetre wave generators (Soviet-made G4–141, G4–142, R2–68, R2–69) were used for medical purposes.[36,45,58,96] These devices are capable of producing either a tuneable fixed-band output (G4 series) or sweeping a signal within a set range of frequencies (R2 series).

Later, generators designed specifically for medical purposes appeared. They produced either a fixed frequency signal or a broad-band low-power noise in the millimetre range. Medical generators such as the Elektronika KVCh[36,40] and Yav[62,64,77,97] were equipped with the generating heads emitting signals at one of the 'therapeutic' frequencies. Broad-band generators such as the Porog[36,43] are characterized by a very low power, and, theoretically, the patient is supposed to react only to certain resonance frequencies.

During MW therapy, the average power density incident to the skin of the patient is below 20 mW/cm^2.

These features of medical MW generators are characteristic of newer devices as well, and the major trends in the modern and prospective models are miniaturization and a higher level of computer control of wavelength, duration of exposure, and continuous or modulated signal output. With the demand for medical generators still high, there are now more than 100 models of medical MW generators on the market in the former USSR and some European countries. The smallest models are the size of a 25-cent coin, and some of the Russian firms, which previously were pre-eminent in military electronics, are now involved in the development and production of these devices.

Conclusions

The therapeutic potential of MW therapy appears very promising. Our experimental results[29–33,70,85] are consistent with the Russian literature and with the model of the therapeutic process that we have developed. However, only appropriate clinical trials can provide a definitive answer regarding the efficacy of MW for medical purposes. Such trials should be conducted in a rigorously controlled double-blind manner. If and when proven effective in independently-controlled double-blind trials, MW therapy may become an inexpensive and non-invasive adjunct therapy or even a monotherapy for some diseases.

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