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THERAPEUTIC, RESTORATIVE AND BIOTECHNOLOGICAL RESOURCES OF SCIENTIFIC MUSIC THERAPY IN SOLVING INFERTILITY PROBLEMS

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Abstract

Scientific music therapy is an advanced therapeutic and preventive direction, widely in demand in various areas of health care, psychological assistance, and social rehabilitation, but still underestimated in reproductive medicine. Complex scientific research conducted over thirty years has helped to better understand the nature of the main mechanisms of music's influence on the neuroendocrine system, vital organs, and cellular structures. On this basis, unique and effective methods of scientific music therapy and promising biotechnologies have been created, the possibilities of which in solving infertility problems are discussed in this article.

Key words: reproductive medicine, infertility, stress, psychotherapy, algorithms, music therapy, cellular acoustics

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ЛЕЧЕБНО-ВОССТАНОВИТЕЛЬНЫЕ И БИОТЕХНОЛОГИЧЕСКИЕ РЕСУРСЫ НАУЧНОЙ МУЗЫКОТЕРАПИИ В РЕШЕНИИ ПРОБЛЕМ БЕСПЛОДИЯ

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Аннотация

Научная музыкотерапия — передовое лечебно-профилактическое направление, широко востребованное в различных областях здравоохранения, психологической помощи и социальной реабилитации, но

пока недооцененное в репродуктивной медицине. Комплексные научные исследования, проводимые в течение тридцати лет, помогли глубже понять природу основных механизмов влияния музыки на нейроэндокринную систему, жизненно важные органы и клеточные структуры. На этой основе созданы уникальные по эффективности методы научной музыкотерапии и перспективные биотехнологии, возможности которых в решении проблем бесплодия и рассматриваются в данной статье.

Ключевые слова: репродуктивная медицина, бесплодие, стресс, психотерапия, алгоритмы, музыкотерапия, клеточная акустика

INTRODUCTION

Impaired reproductive function is one of the pressing problems of our time. According to the World Health Organization, infertility is defined as the inability of a married couple to conceive a child within 12 months of regular sexual intercourse without contraception. It affects every sixth person of reproductive age on the planet, which has a sharply negative impact on the global social and demographic situation. [1].

In this regard, the diagnosis and treatment of infertility is one of the priority areas of reproductive medicine.

Numerous factors play a critical role in the development of this pathology: anatomical, age-related, hormonal, immune, and mental disorders.

Infertility treatment may involve surgical and medicinal methods, psychotherapy, as well as assisted reproductive technologies in the form of artificial insemination, in vitro fertilization, etc. The choice of therapeutic strategy and tactics is dictated by the etiological and pathogenetic factors that caused the reproductive dysfunction in each specific case.

Thus, in cases of infertility caused by emotional disturbances, the cause of which is especially often associated with stress, the use of psychotherapy is indicated.

It has been established that long-term stress can cause various neuroendocrine disorders: in women, hyperprolactinemia, irregularities in the menstrual cycle, or its complete cessation; in men, a decrease in testosterone levels and sperm count.

In general, such changes lead to suppression of the reproductive system, which is manifested by a decrease in sexual activity and infertility [2, 3].

The state of inability to conceive a child often causes secondary emotional disorders, which also require the use of methods of mental correction, among

which the possibilities of music therapy have begun to attract attention.

Thus, in an article by employees of the Human Reproduction Laboratory at the University Clinical Hospital of the city of Goiânia (Brazil), it is noted that women suffering from infertility are often under the pressure of negative experiences, leading to stress.

Meanwhile, according to numerous pieces of literature data, music therapy is an effective resource for treating stressful conditions in various cases. That is the basis for its use as an auxiliary method for restoring reproductive function [4].

Music therapy has been shown to reduce anxiety and pain, and increase satisfaction in infertile women undergoing in vitro fertilization. Moreover, there was a trend toward increased clinical pregnancy rates in such cases, but without statistical significance, requiring further studies with larger sample sizes [5].

However, there are very few works in the published scientific literature devoted to the use of music therapy specifically in reproductive medicine, despite the obvious appropriateness of this approach.

In our opinion, this is due to the lack of a clear understanding of the mechanisms of music therapy in Western schools. Therefore, the research topics are narrowed mainly to studying the influence of empirically selected music on anxiety and the quality of life of patients.

Meanwhile, the healing resources of music therapy have significantly broader possibilities, which are convincingly demonstrated by the achievements of the Russian scientific school.

ON THE DEVELOPMENT OF MUSIC THERAPY

The fact that music influences a person was clear to ancient doctors, according to numerous historical documents. However, only in the second half of the 20th century did music and medicine fully integrate, resulting in the emergence of a new profession — music therapy, which received state recognition, first in the USA, then in England and Germany. [6].

Currently, music therapy methods are widely used in institutions all over the world in various fields of human activity: psychology, clinical medicine, social rehabilitation, etc. [6, 7, 8].

At the same time, two main directions of music therapy have formed in the world system: traditional, based on an intuitive-empirical approach, and scientifically proven, characteristic of the Russian school, the beginning of which

was laid in the 19th century by the works of scientists I.M. Dogel, I.R. Tarkhanov, V.M. Bekhterev and others [9,10,11,12,13].

However, the comprehensive development of scientific music therapy began in Russia in the early 1990s, with clinical studies by the author of this article and his followers.

Since then, over three decades of targeted research by representatives of the Russian school of scientific music therapy have produced more than 450 scientific publications have been produced in the fields of medicine, biophysics, and psychology, including books, monographs, and textbooks. Candidate and doctoral dissertations have been defended, and 11 patents for inventions have been received.

Since 2003, after the Russian Ministry of Health approved the manual for doctors «Methods of Music Therapy», this area has received scientific recognition and official permission for use [14].

Thus, it was established that auditory acoustic impact has a significant impact on brain activity, psychological status and the physiological state of vital systems.

Moreover, the consequences for the body can be both positive and negative, depending on the tempo-rhythmic and acoustic characteristics of the music, as well as on the individual and personal characteristics of the recipient.

The Scientific Music Therapy School (SMT) has developed a whole line of advanced intellectual and technological products:

- fundamental scientific and theoretical base;
- 25 innovative methods and technologies;
- more than 50 digital music therapy programs;
- three hardware and software systems,
- a robot for rehabilitation with a music therapy option.

This became possible thanks to an understanding of the mechanisms by which music influences the body.

The presence in modern music therapy of an interdisciplinary scientific and theoretical base with a wide range of methods and technologies has created a need to create adequate programs for the professional training of specialists.

An important indicator of international recognition of the scientific achievements and educational programs of the NMT school are the numerous foreign publications indexed in Scopus and Web of Science systems. They were published in reputable publishing houses in Germany, Norway, Italy, Hong Kong,

Canada, Great Britain, the USA, including Springer Nature, Chapman and Hall/CRC, etc.

POSSIBILITIES OF USING RECOVERY RESOURCES OF SCIENTIFIC MUSIC THERAPY IN REPRODUCTIVE MEDICINE

The main doctrine of scientific music therapy is the neurohormonal resonance theory, which, for the first time, gave a comprehensive scientific understanding of the mechanisms of the influence of music on a person. [15].

According to this theory, music has a complex multi-level effect on the body, influencing the organs of hearing, skin, and internal organs.

This causes a number of psychosomatic reactions.

1. The organs of hearing generate neurohormonal reactions.
2. The impact of sound on skin receptors, including acupuncture points, triggers starts analgesic and physiological reactions. At the same time, the skin, as a piezoelectric membrane, transmits part of the acoustic energy converted into electromagnetic waves inside.
3. Internal organs react by changing their functional activity under the influence of wave-resonant frequencies.

The data revealed on the patterns of influence of music on the neuroendocrine system, the main coordinator of the body's vital functions, regulating the functions of all organs and systems, turned out to be critically important.

Based on the physical and dynamic analysis, three main acoustic algorithms of influence were identified in the course of experimental studies, regardless of the genre of music. They were called algorithms-regulators with the abbreviations S, HR, and T, since each of them causes characteristic changes in the state of the nervous system and the level of hormones in the blood [15].

The S-algorithm is characterized by softness of sound, slow tempo and low level of acoustic intensity. It reduces the level of cortisol in the blood (stress hormone), inhibits the activity of the cerebral cortex and has a sedative effect.

The T-algorithm is characterized by a fast tempo, energetic sound, and a high sound pressure level. This effect activates the nervous system, simultaneously increasing the level of adrenaline in the blood, as well as the level of β -endorphin, a hormone with a strong analgesic effect.

The HR algorithm has average rates for the tempo and intensity of sound intervention, which occur stabilization in the activity of the nervous system, and

the level of hormones in the blood tends to average normal values, which generally has a beneficial effect on the body and triggers homeostatic recovery mechanisms.

The discovery of the acoustic-physiological laws of the influence of music on the human body became the basis for the development of more than 50 innovative algorithmically organized methods and digital technologies of music therapy. They have become an effective tool for managing vital functions.

Let's look at some methods that can solve problems in reproductive medicine.

1. Musical audio psychotherapy (MAPT)

This method is one of the most accessible and consists of listening to music programs specially developed for psychotherapy, recorded on CD or other digital media (Fig. 1).

List of programs:

№1 "Antistress & Insomnia"

№2 "Easy Breathing & Neurasthenia"

№3 "Vascular Dystonia: Hypertension & Hypotension"

№4 "Mental Health and Development"

№5 "Depression & Overwork"

№7 "Energy +"

№8 "Therapy of Fear and Anxiety"

№9 "Hypertension & Nervous Overstrain"



Fig. 1. Session of musical audio psychotherapy

Рис. 1. Сессия музыкальной аудио-психотерапии

The names of the programs indicate the areas of application. At the same time, MAPT has proven itself in clinical practice as a simple and effective method of

psychotherapy, used in medical and preventive institutions in dozens of countries around the world.

2. Virtual Music Art Therapy (VMART)

VMART is a set of 8 innovative digital programs for audiovisual psychotherapy. It combines two therapeutic factors simultaneously: painting (Van Gogh, K. Monet, I. Aivazovsky, etc.) and music (W. Mozart, P. Tchaikovsky, etc.) masterpieces. Here, for the first time, the principle of algorithmic congruence of sound and visual images is applied, providing the highest possible therapeutic and restorative effect.

Indications for use: psychosomatic disorders, chronic stress, insomnia, fatigue, depressive disorders, decreased reserve capacity of the body, emotional disorders, memory disorders, etc.

The synergy of the positive properties of music and painting provides psychological healing, aesthetic pleasure, knowledge, and development within the framework of one technology, which is equally effective in working with both adults and children.

3. Meso-Forte therapy (MFT)

MFT is a high-tech method of stress management, neurorehabilitation and anti-aging therapy.

To implement this technology, a hardware, and software complex is used with a computerized workstation, an audio system, a patented acoustic wave converter mask, and 38 algorithmically organized digital music therapy programs (Fig. 2).

In MFT, simultaneous musical and acoustic effects on the organs of hearing, reflexogenic zones of the head and skin are used for the first time [15, 16].



Fig. 2. *Meso-Forte Therapy session and hardware-software complex*

Рис. 2. *Сессия Мезо-Форте терапии и аппаратно-программный комплекс*

The resulting effects: MFT optimizes the level of hormones in the blood, stabilizes the emotional state, makes the skin smooth, causes external and internal regenerative reactions.

PROMISING PROJECTS FOR REPRODUCTIVE MEDICINE

1. Opening of digital music and art therapy rooms in reproductive health centers

The effectiveness of using digital technologies of music and art therapy in the treatment of neurotic and psychosomatic disorders, stress conditions, pain syndromes, etc., has been confirmed in clinical studies [15, 16, 17].

In this regard, there is no doubt about the advisability of opening digital music and art therapy rooms for the practical application of accumulated experience in reproductive health centers (Fig. 3).



Fig. 3. *Digital Music & Art Therapy room*

Рис. 3. *Кабинет цифровой музыкально-арт-терапии*

The basic list of equipment and programs for the office may vary depending on the profile of a particular institution.

Technical support:

- Computerized workplace
- Digital psychotherapy kit "Music of Health"
- Hardware and software complex "Meso-Forte"
- "Virtual music-art therapy" kit

➤ Audiovisual system.

Digital music and art therapy rooms can provide high-tech psychological assistance and rehabilitation treatment aimed at combating stress, emotional, and hormonal disorders in people suffering from infertility, at a minimum, enhancing other treatment methods, and at a maximum, completely solving the existing problem.

The undoubted advantages of digital offices include the computerization of services provided, which allows them to be performed after short-term advanced training courses for a wide range of specialists.

2. Musical and acoustic biotechnology in the treatment of infertility

In the second half of the 20th century, thanks to scientific and technical progress, as well as the successes of scientific music therapy in practical medicine, interest in studying the influence of acoustic effects on the human body and biological objects increased. Evidence appeared of the influence of music not only on vital organs and systems, but also on cellular structures.

Thus, a new scientific direction was born called cellular acoustics. This term was proposed in 1999 [18].

The main goal of cellular acoustics was defined in the direction of studying patterns of musical-acoustic effects with the search for regulatory algorithms for their subsequent use in medicine and biotechnology.

It was a long series of experiments with different models of cell cultures in vitro (1996–2022). It was revealed that acoustic signals were able to activate or suppress the vital activity of cells. That was dependent on the algorithms of acoustic action [18].

It has been established that certain types of musical influences, called genetically affiliated, activate DNA structures and cause cell proliferation.

Bioacoustic research related to blood, in particular, leukocytes and stem cells, has been particularly fruitful. In 2003, we succeeded in creating a program with a regenerative musical-acoustic algorithm.

Direct transmission of this program to blood in vitro allowed to increase the total number of leukocytes by 4.7 times, neutrophils by 4.7 times, lymphocytes by 3.9 times in one hour. A particularly pronounced effect was found in immature granulocytes (ImGr), the number of which increased by 18.3 times ($P < 0.001$). This method of complex blood correction was patented [19].

It is obvious that the leukocyte mass grew in the experiment both due to bioacoustic activation of mature blood cells and hematopoietic stem cells, causing

their intensive proliferation. These results suggest that regenerative acoustic biotechnologies may be very useful in reproductive medicine.

Direct experimental evidence began to appear that was in line with this thesis. For example, researchers from Monash University in Australia used ultrasound waves to improve sperm motility. It was found that exposure to ultrasound at a frequency of 40 MHz and a power of 800 mW for 20 seconds increased sperm motility (their swimming ability) by 266% and reduced the proportion of inactive sperm from 36% to only 10% [20].

In 2018, Swedish scientists demonstrated the existence of a helical antenna in the tail of the sperm, which is capable of providing it with resonant interaction with the environment to bypass obstacles, etc. [21].

The use of genetically affiliated music to increase the reduced reproductive potency of spermatozoa seems to be a promising technology for treating infertility.

For this, it is necessary to conduct appropriate studies.

CONCLUSION

Scientific music therapy has effective, clinically proven therapeutic and restorative resources, as well as international recognition, which is confirmed by numerous foreign publications indexed in Scopus and Web of Science systems, published in reputable publishing houses in Germany, Norway, Italy, Hong Kong, Canada, Great Britain, and the USA, including Springer Nature, Chapman and Hall/CRC, etc.

Open acoustic-physiological mechanisms of musical effects reflect the general principles of the body's sensory systems and are therefore universal. Algorithmically organized technologies of music-art therapy created on this basis have high potential for successful application in solving current problems of reproductive health.

Moreover, if psychogenic factors underlie infertility, the technologies of scientific music therapy may be the main method of treatment. In other cases, they can be an adjunctive treatment method that will nevertheless combine well with medications and any other methods of restoring reproductive function, enhancing the overall clinical results.

The integration of science, musical art and digital technology opens up promising prospects for medicine in general and reproductive medicine in particular, giving new hope for infertility relief to couples facing this problem.

ADDITIONAL

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Список литературы/References

1. Песуц БОЗ. // URL: <https://www.who.int/ru/news-room/fact-sheets/detail/infertility>. [WHO resource.// Available at: <https://www.who.int/ru/news-room/fact-sheets/detail/infertility>]. (In Russian).
2. Сапольски, Р.М. Психология стресса / Роберт Сапольски; перевод с английского под редакцией профессора Е. И. Николаевой. 3-е изд. Санкт-Петербург: Питер, 2019. - 480 с. [Sapolsky, R.M. Psychology of stress / Robert Sapolsky; translation from English edited by Professor E.I. Nikolaeva. 3rd ed. St. Petersburg: Piter, 2019. - 480 p.]. (In Russian).
3. Смелышева Л.Н., Кайгородцев А.В., Киселева М.М. и др. Влияние эмоционального стресса на показатели репродуктивной функции у студенток. *Человек. Спорт. Медицина*. 2016, Т.1, (1): 5-12. DOI: 10.14529/hsm160101 [Smelysheva L.N., Kaigorodtsev A.V., Kiseleva M.M. et al. The influence of emotional stress on reproductive function indicators in female students. *Human. Sport. Medicine*. 2016, Vol. 1 (1):5-12.]. (In Russian). DOI: 10.14529/hsm160101
4. Eliamar Aparecida de B. Fleury, Mario S. Approbato, Tatiana M. da Silva, et al. Music therapy in stress: proposal of extension to Assisted Reproduction. Federal University of the State of Goiás (UFG). Laboratory of Human Reproduction of

Hospital das Clínicas -Goiânia (GO) - *Brazil JBRA Assisted Reproduction* 2014; 18(2):55-61. DOI: 10.5935/1518-0557.20140006

5. Mahmoud, M. Y., Labib, K., Sileem, S. A., et al. The impact of music therapy on anxiety and pregnancy rate among infertile women undergoing assisted reproductive technologies: a systematic review and meta-analysis. *Journal of Psychosomatic Obstetrics & Gynecology*. 2021, 43 (2):205–213. DOI: <https://doi.org/10.1080/0167482X.2021.1977277>

6. Шушарджан С.В. Руководство по музыкотерапии. М., Медицина, 2005. 478 с. [Shushardzhan S.V. Guide to music therapy. Moscow, Medicina, 2005. 478 p.]. (In Russian).

7. Giordano F, Scarlata E, Baroni M, et al. Receptive music therapy to reduce stress and improve wellbeing in Italian clinical staff involved in COVID-19 pandemic: A preliminary study. *The Arts in Psychotherapy*. 2020 Sep; 70:101688. DOI: 10.1016/j.aip.2020.101688. PMID: 32834302; PMCID: PMC7361107.

8. Mitrovic, P.; Stefanovic, B.; Paladin, A.; Radovanovic, M.; Radovanovic, N.; Rajic, D.; Matic, G. Novakovic, A.; Mijic, N.; Vasiljevic, Z. The Music Therapy in hypertensive patients with acute myocardial infarction after previous coronary artery bypass surgery. *Journal of Hypertension*. 2015 (33):134. DOI: 10.1097/01.hjh.0000467721.68263.92

9. Бехтерев В.М. Вопросы, связанные с лечением и гигиеническим значением музыки. *Обозрение психиатрии, неврологии и экспериментальной психологии*. 1916; (4): 105–124. [Bekhterev V.M. Issues related to the treatment and hygienic significance of music. 1916; (4): 105–124]. (In Russian).

10. Догель И.М. Влияние музыки и цветов спектра на нервную систему человека и животных. Казань, Типо-литография Императорского университета, 1898. 141 с. [Dogel I.M. The influence of music and the colors of the spectrum on the nervous system of humans and animals. Kazan, Tipolitografiya Imperatorskago universiteta, 1898. 141 p.]. (In Russian).

11. Тарханов И.Р. О влиянии музыки на человеческий организм. Санкт-Петербург: тип. В. Демакова, 1893. 62 с. [Tarhanov I. R. About the influence of music on the human body. Sankt-Peterburg: tip. V. Demakova, 1893. 62 p.]. (In Russian).

12. Захарова Н.Н., Авдеев В.М. Функциональные изменения центральной нервной системы при восприятии музыки. *Журнал высшей нервной деятельности*. 1982, Т. XXXII (5): 915- 929 [Zakharova N.N., Avdeev V.M. Functional changes in the central nervous system during music perception. *Journal*

of Higher Nervous Activity. 1982, V. XXXII, (5):915-929]. (In Russian).

13. Могендович М.Р., Полякова В.Б. К физиологическому анализу влияния музыки на человека. Тез. докл. 21 совещание по проблемам высшей нервной деятельности. М., 1966, 204-205 с. [Mogendovich M.R., Polyakova V.B. On the physiological analysis of the influence of music on humans. Abstract. 21st meeting on problems of higher nervous activity. Moscow, 1966, 204-205 p.] (In Russian).

14. Разумов А.Н., Шушарджан С.В. Методы музыкальной терапии (пособие для врачей). М., РНЦВМ и К МЗ РФ. 2002, 29 с. [Razumov A.N., Shushardzhan S.V. Music therapy methods (a manual for doctors). Moscow, RNCVM i K MZ RF. 2002, 29 p.]. (In Russian).

15. Shushardzhan, S.V., Petoukhov, S.V. Engineering in the scientific music therapy and acoustic biotechnologies. In: Hu Z., Petoukhov S., He M. (eds) *Advances in Artificial Systems for Medicine and Education III*. AIMEE 2019. *Advances in Intelligent Systems and Computing*. 2020; 1126:273–282. Springer, Cham. DOI: https://doi.org/10.1007/978-3-030-39162-1_25

16. Shushardzhan S.V., Allik T.L., Eremina N.I. Meso-Forte — Innovative Method for Musical-Acoustic Psychotherapy and Neurohormonal Correction with Anti-Aging Effect: Clinical Study. *Bulletin of Rehabilitation Medicine*. 2022; 21 (1):79-85. DOI: <https://doi.org/10.38025/2078-1962-2022-21-1-79-85>

17. Шушарджан С.В., Еремина Н.И., Гигинейшвили Г.Р., Гилевич М.Ю., Гордеева Т.Ю. Мобильное приложение «My Energy Stream» как цифровая технология рецептивной музыкотерапии невротических расстройств, связанных со стрессом. *Традиционная медицина*. 2022; 4(70):49-54. DOI: 10.54296/18186173_2022_4_49 [Shushardzhan S.V., Eremina N.I., Gigineishvili G.R., Gilevich M.Yu., Gordeeva T.Yu. Mobile application «My Energy Stream» as a digital technology for receptive music therapy for neurotic disorders associated with stress. *Traditional Medicine*. 2022, 4(70):49-54.]. (In Russian). DOI: 10.54296/18186173_2022_4_49

18. Шушарджан С.В., Еремина Н.И. О влиянии музыкально-акустических воздействий на клеточный иммунитет и перспективах биоакустических технологий. *Медицина и Искусство*. 2023, Т.1 (3):94-107. DOI: <https://doi.org/10.60042/2949-2165-2023-1-3-94-107> [Shushardzhan S.V., Eremina N.I. Influence of musical-acoustic impacts on cellular immunity and the prospects of bioacoustic technologies // *Medicine and Art*. 2023, V.1 (3):94-107.]. (In Russian). DOI: <https://doi.org/10.60042/2949-2165-2023-1-3-94-107>

19. Шушарджан С.В., Шушарджан Р.С. Способ активизации роста лейкоцитарной массы и комплексной коррекции состава крови in Vitro: Патент №RU2518534C1 (2014). [Shushardzhan, S.V., Shushardzhan, R.S. The method of enhancing the growth of leukocyte mass and the complex correction of the blood in Vitro. Patent №RU2518534C1 (2014)]. (In Russian).
20. Vafaie, A., Raveshi, M. R., Devendran, et al. (2024). Making immotile sperm motile using high-frequency ultrasound. *Science Advances*, 10(7). DOI: <https://doi.org/10.1126/sciadv.adk2864>
21. Zabeo, D., Heumann, J.M., Schwartz C.L. et al. (2018). A lumenal interrupted helix in human sperm tail microtubules. *Scientific Reports*, 8(1), 2727. DOI: 10.1038/s41598-018-21165-8.