

Editorial

Synergistic Approach: Photobiomodulation, Neuromodulation, and Drug Therapy in Neuropsychiatry. A Promising Strategy to Enhance PBM Adoption and Neurotherapy Efficacy

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Abstract

Photobiomodulation (PBM) is an effective method for treating neuropsychiatric diseases, yet its universal acceptance and utilization remain constrained. In this Letter to the Editor/Expert Opinion, we address the challenges confronting PBM researchers and pioneers, striving to establish universal confidence in its exclusive application for neuropsychiatric patient care. Despite encouraging animal experiments and selecting positive human clinical trial outcomes, PBM's widespread acceptance of PBM is hindered by factors including limited clinical studies and clashes with established therapies, such as drug therapy and psychotherapy.

To overcome these obstacles and broaden PBM's adoption and application of PBM in neuropsychiatry, we propose a combinatorial therapy approach. By integrating PBM with interventions such as Cognitive Behavioral Therapy (CBT) or drug therapy, a cumulative effect can be attained, benefiting both patients and therapists. Patients gain access to diverse treatment options and experience synergistic effects of combined therapies, thereby enhancing outcomes. Therapists benefit from expanded intervention choices and improved quality of patient care.

This study introduces a novel strategy of amalgamating PBM with recognized interventions, such as CBT and drug therapy, to address existing challenges. This combined approach offers a practical solution to augment PBM acceptance and usage in the realm of neuropsychiatry.

To endorse this strategy, a shift in the research direction is imperative. Future studies should investigate the amalgamated use of PBM with other neurointerventions, such as CBT or drug therapy. Robust clinical trials contrasting groups like "PBM + CBT" and "PBM (sham) + rTMS" are vital to persuade clinicians and patients toward embracing combined PBM therapies.

Although PBM's eventual autonomy as a neuropsychiatric treatment is an overarching goal, the present combination therapy approach proves practical, inevitable, and mutually beneficial. By bridging conventional therapies with PBM, this strategy may facilitate wider acceptance and utilization in neuropsychiatry.

Introduction

Transcranial photobiomodulation (t-PBM) employing near-infrared (NIR) light is a promising treatment for psychiatric and neurological conditions [1,2]. Studies on cadavers have confirmed the ability of NIR light to reach cortical brain regions through skull and forehead tissues [3,4]. At the cellular level, red and NIR light stimulates Cytochrome C Oxidase (CCO) within the mitochondrial electron transport chain, with CCO acting as the primary photoreceptor driving various brain effects [5,6]. These effects include ATP production, increased reactive oxygen species, and enhanced cerebral blood flow (CBF) [6]. Clinical trials have revealed the potential of t-PBM in alleviating depressive symptoms. An initial trial involving

individuals with Major Depressive Disorder (MDD) and comorbid anxiety showed reduced symptoms after a single NIR treatment that persisted significantly after two weeks [7]. Another study demonstrated decreased depressive symptoms after six NIR treatments, with good tolerability [8]. Similarly, eight weeks of twice-weekly NIR t-PBM sessions for MDD patients yielded antidepressant effects [9]. The low cost, safety profile, and ease of administration position t-PBM for broad accessibility [10].

For several decades, PBM has been presented as an effective method for treating neuropsychiatric diseases. Various research and grants in PBM, especially in the field of neuropsychiatry, have been conducted or are ongoing.

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Submitted: July 28, 2023

Approved: August 17, 2023

Published: August 18, 2023

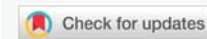
How to cite this article:

Vahedifard F. Synergistic Approach: Photobiomodulation, Neuromodulation, and Drug Therapy in Neuropsychiatry. A Promising Strategy to Enhance PBM Adoption and Neurotherapy Efficacy. *J Neurosci Neurol Disord.* 2023; 7: 057-060.

DOI: 10.29328/journal.jnnd.1001079

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Keywords: Photobiomodulation; PBM; Psychotherapy; Recurrent transcranial magnetic stimulation (rtms); Mental health





Despite the decades since the introduction of the PBM, there is still hesitation about general acceptance and overall usage.

At present, researchers and pioneers of PBM have to answer a fundamental question: How much do physicians or patients now trust in treating their patients - depression, Alzheimer's, or other situations with PBM affects them - exclusively with PBM? Consider a depressed patient who has had difficulty being accepted by a family member or physician to receive treatment. Patients may experience exacerbation, relapse, recurrence, or even suicide at any stage of depression. Is there sufficient confidence and credibility to use PBM exclusively in such patients? Do therapists, who are always concerned about patients' lack of treatment and legal medical issues, already have the complete confidence to be content by applying PBMs exclusively to patients? Is there acceptance among medical insurance companies to provide coverage for this management plan, only with PBM? Finally, does the current widespread use of PBM seem satisfactory?

The logical answer to these questions seems to be "No" at the moment. Several animal experiments have been performed on PBM. In addition, meaningful effects of PBM on blood circulation, oxygenation (bold signal), and neurophysiological data (EEG) have been shown. In some human clinical trials, the use of PBM improved patients' neuropsychiatric symptoms. However, this seems to be an overlooked item, leading to PBM not being universally accepted by psychiatrists, other specialists, general practitioners, patients, and families. There are several reasons for this lack of universal use of PBM.

1- Insufficient number of clinical studies indicating the effects of PBM. However, many studies have been published regarding PBM or are currently in progress. Therefore, the number of articles may not be a solution, but their orientation should be changed.

2- The scientific conflict and conflicts of interest for the widespread use of PBM (especially in exclusive form) are present among clinicians, medical companies, insurance, and patients. The majority of treatments for neuropsychiatric patients (especially depression and Alzheimer's disease) are based on drugs and psychotherapy. In addition, drug therapy is supported by the efforts of many clinicians, researchers, and large pharmaceutical companies, and psychotherapy has countless therapists, researchers, and fans among clients. In the face of these entrenched modalities, proposing and using new therapeutic modalities in neuropsychiatry will undoubtedly lead to resistance to expansion, promotion, recommendation, and consumption.

3- The third reason, which may result from the previous two causes, is the lack of investigations on the combined use of PBM, in the form of PBM + CBT or PBM + Drug therapy. The answer to this third question may also solve the main problem.

- Therefore, the answer to the main problem can be found in this solution: augmentation therapies and therapists

[11,12]. As PBM researchers, we must now consider an agglomerative effect. By achieving the cumulative effect of PBM-CBT, all components of the treatment team, specifically the patient, will have augmented and new advantages. Patients will benefit more from treatment because of the separate effects of each intervention, the synergistic effect, and the diversity and variety of treatment options.

- Therapists and clinicians (specialists or primary care professionals) will also be more satisfied with the increase in intervention options and the improvement of their patients.
- As a result, companies and startups related to PBM can produce and supply more devices with increased use of PBM. First, increased production and sales provide the goal of expanding PBM and will provide more data and therapeutic feedback to PBM researchers and therapists. It also provides researchers with financial opportunities to develop up-to-date devices and support PBM research.

However, to expand the combination use of PBM-CBT or PBM-drug therapy in clinics, we need a change and significant shift in the direction of applied and clinical research on PBM. According to a literature review, almost all the examined PBM effects were individually and isolated, not combined with other interventions (such as CBT, or Drug therapy). In most animal, laboratory, imaging, and clinical studies, the primary focus was PBM evaluation in the Sham and Case groups. In almost no study, the effect of the combined use of PBM with medication or psychotherapy has been investigated, especially in large populations. The lack of these types of studies and evidence led to a lack of persuasion among clinicians to prescribe PBM and for patients to use them. It seems that the research path should change from examining isolated PBM to combining PBM with other neuro-interventions. For these studies, different groups of patients were suggested, for example:

1. "PBM + CBT" versus "PBM (sham) + Repetitive transcranial magnetic stimulation (rTMS)"
2. "PBM + CBT" versus "PBM (sham) + CBT"
3. "PBM + CBT- i (Internet-based)" versus "PBM (sham) + CBT- i"
4. "PBM + Drug therapy" versus "PBM (sham) + Drug therapy"
5. "PBM + Drug therapy" versus "PBM (active) + Drug therapy (Placebo)"
6. "PBM + CBT" versus "PBM (active) + Drug therapy"
7. "PBM + CBT" versus "PBM (active) + CBT- i"

We advocate a paradigm shift in research focus to address the dearth of evidence supporting the combined use of PBM with other interventions. Instead of isolating PBM effects, future studies should investigate the synergistic outcomes



of integrating PBM with established treatments, such as Cognitive Behavioral Therapy (CBT) or drug therapy.

By exploring various patient groups and clinical contexts, such as 'PBM + CBT' versus 'PBM (sham) + Repetitive transcranial magnetic stimulation (rTMS),' we can ascertain combined PBM therapies' efficacy and potential advantages.

It will also be helpful to select the case groups precisely from the same routine groups seen in therapeutic practice, such as hospitalized patients, patients referred to a psychiatric clinic or primary care, and outpatient treatment at home. This case selection, which is more tangible and closer to practice, will be more convincing for physicians, patients, and medical companies to combine the use of PBM.

As a long-term goal, PBM can be used as an independent neuropsychiatric treatment option. However, combining PBM with other interventions is an exciting, effective, compelling, inevitable, and win-win approach. A modest peace between different therapies, yet bold, to further expand PBM.

Bridging the gap between existing therapies and PBM requires a comprehensive examination of this approach's benefits, limitations, and ethical considerations [13,14]. This manuscript aims to shed light on the potential of combined PBM therapies and their implications in neuropsychiatric practice. In this capacity, the following points should be considered.

1. "The integration of PBM into the treatment landscape of neuropsychiatric disorders, such as depression and Alzheimer's disease, necessitates rigorous clinical trials that encompass a wide range of exposure times and laser wavelengths. This multifaceted approach aims to uncover the optimal parameters for achieving therapeutic effects."
2. To comprehensively assess the impact of combined PBM interventions, it is imperative to introduce innovative biomarkers capable of capturing the dynamic changes in vascular hemodynamics and redox activity of the mitochondrial respiratory chain. This shift towards in vivo measurements allows for a more nuanced understanding of the underlying mechanisms at play."
3. "The strategic implementation of a broadband near-infrared (NIR) spectroscopy system empowers researchers to investigate intricate changes within the cerebral microenvironment. By closely monitoring variations in oxygenated hemoglobin ($\Delta[\text{HbO}]$) and oxidized cytochrome c oxidase ($\Delta[\text{oxCCO}]$), this spectroscopy approach offers valuable insights into the immediate and sustained effects of PBM on neurovascular function."
4. "The comparison of these biomarker responses between the experimental group undergoing combined PBM and the placebo group is poised to unravel the

true potential of PBM's therapeutic benefits. This comparative analysis extends beyond traditional outcome measures, shedding light on the intricate interplay between light-mediated stimulation and neuropsychiatric pathophysiology."

5. "Ultimately, the judicious utilization of multiple lasers at distinct wavelengths and LED further enhances the precision of this investigation. These diverse light sources contribute to a comprehensive exploration of PBM's impact, aligning with the complex nature of neuropsychiatric disorders and the intricate network of biological processes they entail."
6. "Through meticulous clinical trials and the incorporation of innovative measurement techniques, this research venture endeavors to forge a path toward a deeper comprehension of the synergistic effects of combined PBM interventions. Such insights can potentially revolutionize the therapeutic landscape for patients grappling with neuropsychiatric conditions, offering novel avenues for effective intervention and improved quality of life."

Ethical concerns regarding PBM combinations

1. "Expanding on the insightful points raised, the ethical dimensions surrounding the incorporation of PBM in general practice deserve thoughtful exploration. The evolving landscape of medical innovation underscores the critical importance of striking a harmonious balance between technological advancement and the meticulous accumulation of clinical evidence."
2. "In light of these concerns, it is imperative to delve into ethical considerations about introducing PBM therapies before robust clinical trials substantiate them. The complexities surrounding neuropsychiatric disorders demand that we proceed with due diligence, ensuring that the introduction of innovative modalities aligns with the highest standards of patient care."
3. "Moreover, international discourse on defining the optimal parameters for PBM, measuring its efficacy, and deciphering its mechanisms underscores the need for a comprehensive understanding before widespread application. Ethical considerations extend beyond the safety and efficacy of interventions; they encompass the integrity of medical practice and the well-being of patients."
4. "Engaging in a transparent and inclusive dialogue surrounding the ethical dimensions of integrating PBM therapies into general practice is paramount. Such discussions foster an environment where a collective commitment to both scientific rigor and the welfare of patients drives advancements."



5. “The evolution of PBM from a promising concept to a clinically validated therapy must be navigated with an unwavering dedication to patient-centered care. As such, candid conversations concerning the ethical implications of introducing this technology without adequate trials are pivotal in shaping the responsible adoption of innovative treatments in neuropsychiatric care.”

Conclusion

PBM has emerged as a promising avenue for addressing the challenges posed by neuropsychiatric disorders. Despite decades of research and grant funding, its widespread adoption in clinical practice remains elusive. This reluctance can be attributed to a confluence of factors, including the absence of robust clinical studies showing its efficacy, conflicts of interest among stakeholders, and the lack of investigations into its combined utilization with established interventions, such as Cognitive Behavioral Therapy (CBT) or pharmacotherapy.

We propose an innovative approach that integrates PBM with existing therapies to overcome these hurdles and forge a path toward broader acceptance and implementation. By combining the targeted effects of PBM with the established benefits of CBT or drug therapy, a synergistic effect is generated that can significantly enhance patient outcomes. This approach addresses immediate challenges while also contributing to the gradual establishment of PBM as a stand-alone treatment.

This integrative strategy not only offers clinicians an expanded arsenal of therapeutic tools but also addresses the concerns surrounding PBM’s credibility and efficacy of PBM. By designing and conducting extensive clinical trials to examine the collective impact of PBM and established interventions, we can amass the compelling evidence required to convince both clinicians and patients of its merits.

Furthermore, adopting combination therapies can increase device production and supply, thereby nurturing further research and development in the field. The financial support generated from utilizing PBM-combination therapies can be reinvested in refining the PBM technology and expanding its applicability.

In conclusion, the combination of PBM with established neuropsychiatric interventions represents a pragmatic and potent solution to the challenges facing PBM’s integration of PBM into clinical practice. By creating a pathway that offers both immediate benefits and long-term potential, this strategy serves as a bridge between innovation and acceptance, pushing the boundaries of neuropsychiatric treatment while propelling the field toward a more promising future.

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