

Peer Review File

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Round 1

Reviewer A

In all, the authors intended to determine interest in various second line therapy for ED and investigate Internet search interest in various wave therapy. The introduction of GAINSWave has been problematic for urologists counseling patients, as patients anticipate dramatic results with an investigational treatment, as mentioned by the authors. The study offers some interesting findings to the community regarding the degree of interest and the diffuse penetration of market advertising by GAINSWave since its introduction.

This manuscript should aim to emphasize the more appropriate forms of focused LiESWT in comparison to radial or acoustic wave techniques. While the jury is still out, this technology potentially offers a more viable alternative despite the need for more rigorous study. As mentioned, discouraging the use of misinformed treatment is important, but offering an alternative to maximize patient benefit is also essential in maintaining them under expert care. More information about focused LiESWT should be included in the discussion of the paper as this may be the direction patients could be sent in the future.

As expected, invested money in marketing as with the GAINSWave platform does lead to additional hits as ICI and IU do not have any financial incentive to advertise. The authors should go into more detail about the different shockwave techniques and variability in their success rates.

The study is very well written. Of note, the titles of the figures (1 and 2) should be switched to represent the attached data. This should be reviewed throughout the manuscript, as the figures are referenced for content at multiple points in the results section.

Response A: Hello, we would like to sincerely thank you for your detailed comments and suggestions. You raise a very valid point in that while LiSWT is still a new technology being researched, it does provide a potential viable alternative or supplementary treatment that is distinct from acoustic wave therapy. We do mention that there has been preliminary data done regarding LiSWT in lines 271-272 and 291-293. We will add a more extensive section in the discussion strongly distinguishing LiSWT from its counterparts and its potential for use as a viable second-line therapy.

Additionally, regarding the second point, we agree that it is important to tabulate the different types of shockwave treatment and variable success rates. While our paper aims to focus on general population-level interest trends in PRP and shockwave therapy and reasons for this, we agree that it is beneficial to include information specifically regarding the potential benefits of LiSWT and have done so accordingly. We note that a more extensive conversation focusing specifically on the different classes and efficacies of shockwave therapy would be

well-suited for a distinct review paper.

Changes in text:

The titles for Figures 1 and 2 have been revised accordingly and cross-referenced through the study.

Lines 306-320 on Page 14 now extensively discussing the efficacy of LiSWT and the distinction between LiSWT and radial wave therapy, as well as referencing a new 2022 study published in the Journal of Urology which shows efficacy of LiSWT. The text now reads: “As such, we believe that direct-to-consumer marketing is a key factor in driving population-level interest in these restorative therapies for ED. It is important to note that despite its current “experimental” status, focused LiSWT appears to have the potential to become an accepted and viable second-line therapy. (26) Recently published papers in the field of urology specifically support the efficacy of focused LiSWT, rather than unfocused acoustic/radial shockwave therapy. While all forms of shockwave therapy inherently use acoustic or sound waves as their modality of treatment, radial wave therapy and focused shockwave therapy use distinctly different methods of sound waves. Focused LiSWT employs a similar mechanism to the shockwave lithotripsy used in the treatment of urolithiasis, which sends out acoustic waves that can be directed and focally penetrate to a greater depth. (29) In contrast, radial wave therapy utilize acoustic waves that disperse outwards and penetrates to a shallower depth than focused LiSWT. (29, 30) In recent literature, Kalyvianakis et al performed the first rigorous double-blind randomized, sham-controlled study to evaluate the efficacy of focused LiSWT on patients with moderate vasculogenic ED. (31) Their findings excitingly suggest that there is strong evidence of efficacy of LiSWT in treating vasculogenic ED.”

Added lines 323-325 on page 14 expanding on the importance of educating patients on the difference between the types of shockwave therapy: “As research continues to illuminate the efficacy and safety of LiSWT, it is more important than ever for urologists to make the distinction between the types of shockwave therapy clear to their patient population.”

Reviewer B

1. Your title states “restorative therapies in ED”- is PDE5i/ICI/VED actually restorative or merely treating the symptoms of ED? Restorative therapy would be angioplasty/arterial reconstruction, cellular-based technology and shockwave therapy although tadalafil daily therapy may fit this description too.

2. In your objective statement- “Our goal is to better understand what factors may influence population-level interest in non-first-line therapies for ED and whether this interest corresponds with AUA and SMSNA guidelines regarding ED treatment”. However, I fail to see/read what are the factors that drive internet search? Is it marketing (bias or factual information), cost of treatment, demographic etc.? What is/are the driving force(s) for internet search?

3. What was the decision to stop tabulating the outcome in March 2020? Surely, it would be more interesting to see if the COVID pandemic impacts the internet search since most males

will be confined at home and studies showed an increase in psychosexual issues during this pandemic.

4. You forgot stem cell therapy- this is very different to PRP.

5. Selected variables- I would like to see a more in-depth analysis on these- breakdown PRP, shockwave machines etc. Also, the demographics of users should shed some interesting findings too.

Response B: Hello, we want to sincerely thank you for your detailed comments and hope to have individually addressed them as below.

1. Your point is well taken—the title of our paper is more in reference to SWT and PRP as the striking finding of our search is the level of interest in said therapies as a result of direct-to-consumer marketing. PDE5i/ICI/VED, on the other hand, are the evidence-backed, non-restorative standard treatments that we included in our initial Google Trends search to serve as a baseline comparison to the newer restorative treatments, as listed by the SMSNA. We recognize that the title may not have been as clear as we intended, so we added “non-restorative” in line 96 and “or restoration” in line 101 to make the distinction clearer.

2. While there are numerous factors that influence population-level interest in these non-first-line therapies of ED, we believe that marketing platforms may be driving a current upward trend in interest. We have added lines 306-308 to more explicitly state our belief that direct-to-consumer marketing is a key factor in driving population-level interest. We agree that other factors you mention including cost of treatment and demographics play a role, but we believe that is a topic that is better suited for a separate study, as Google Trends itself is not able to capture these concepts as readily. As we mention in point 5, the constructive feedback provided have helped focus a new project we are now working on that assesses more patient-level factors including cost of treatment and type of provider.

3. We were trying to capture the general market trends over the past decade and agree that COVID-19 may have likely altered this course. Given the inherent limitations of Google Trends, including being unable to specify demographics and other identifying information, we understand that there are multiple confounding factors associated with our study. As such, we wanted to limit as many other confounding factors as possible, COVID-19 being a powerful one. However, we do believe this would be well-suited for a targeted paper specifically looking at how the increase in psychosexual issues in the pandemic may have impacted general population-level interests.

4. We recognize that stem cell therapy is yet another restorative/regenerative therapy that is gaining interest and popularity and is often offered at the same clinics that provide PRP and acoustic wave therapies. However, for this paper, there were specific limitations of the Google Trends search engine that drove our decision. Preliminary searches revealed that stem cell therapy for ED had such a relative lack of search interest (orders of magnitude smaller) that it did not register on the scale when compared to PRP, SWT and the guideline backed, traditional 2nd line therapies. As such, we decided to focus specifically on PRP and shockwave

therapy given the notable levels of popularity amongst the general population.

5. We agree that more detailed breakdowns do provide more information. However, Google Trends is limited based on both word count and a maximum of 5 unique search items per single comparison. Another limitation of the google trends search function, is that it unfortunately does not provide us with the demographics of users. This limitation is now discussed explicitly in the limitations of our study, lines 339-342.

Your feedback has prompted a new project is to more rigorously evaluate the public information available on the direct-to-consumer clinic websites that advertise regenerative therapies for ED. This will focus on characterizing shockwave machine types, PRP protocols, and demographic characteristics. We will also plan to grade the health information on this site via the DISCERN criteria.

Changes in text:

As detailed in the responses above.

Reviewer C

The manuscript titled as “Restorative Therapies for Erectile Dysfunction: The Influence of Direct-to-Consumer Marketing on Patient Interest” is an interesting study about users’ Web search habits for patients with ED, which gives us an unique perspective on what ED patients searched. Interesting study and good job. I would be very happy when I read this kind of report in leisure time. However, I would frown, if I read it when I got a professional journal. This reports should be published in general media rather than a special urological journal. This work should and must be done by manufacturers instead of urologists.

Response C:

We appreciate your comments and thoughts on the nature of our research and thank you for your comments. Respectfully, our team feels that understanding what patients desire in treatments and what they are being exposed to (especially in the new paradigm of shared decision-making) is paramount. Because of the dramatic effect of consumerization in health-care choices, it is especially vital for urologists to understand the population-level trends of patient interests. As such, we firmly believe that this research does belong in a specialty urological journal. By understanding general interest and market trends, practicing urologists are better equipped to effectively intervene and respond to patient expectations and needs.

Changes in text:

None

Round 2

Reviewer A

This study is an infodemiologic investigation of direct-to-consumer marketing on search trends for nonoperative, non-oral treatment for erectile dysfunction. The stated objectives of this study

are to:

1. Understand what factors may influence population-level interest in “non-first-line therapies.”
2. Understand whether the generated interest corresponds with AUA and SMSNA guidelines for ED treatment.
3. Quantify the frequency of internet search queries for “restorative” ED therapies in order to characterize the impact of direct-to-consumer marketing in the field.

The most important revision needed for this study is removal of the terminologies “first-line” and “second-line” for ED therapies. All of the AUA guidelines/recommended therapies for erectile dysfunction are now considered “first-line” and should be arrived at via a shared decision-making pathway (see attached algorithm).

Regarding the aforementioned objectives:

1. It remains unclear exactly what factors influenced the interest in these alternative therapies. Was it the amount of money spent on marketing? Was it the platforms employed for marketing? Are the makers of low-intensity shockwave therapy not advertising? It is clear that GAINESwave searches increased dramatically, but it is unclear why.
2. Straightforward. It appears that the interest does not correspond with guidelines recommendations.
3. It is unclear what the impact of the D2C marketing has had on the field from this study. It is clear what impact it has had on searches, but it would be more compelling to show where dollars are going as a result of this marketing. Sure, more people are searching GAINESwave, but are more people spending money on this therapy? Are they spending less money on more “traditional” therapies? Have there been any studies on the efficacy of GAINESwave?

Small critique: Line 301, “authentic shock therapy” – “Authentic” does not seem like the right word for an investigational therapy. I would just leave it as LiSWT or the like. Similarly, “restorative” therapies also does not seem quite right for the therapies in this study.

Response A: Thank you for your comments. We have revised our manuscript appropriately, removing “first-line” and “second-line” and rather, discussing the AUA guideline therapies using the shared decision-making pathway as stated before.

1. We feel that this paper highlights a clear factor that influences patient interest in these alternative therapies: direct to consumer marketing. GAINESwave itself is a provider database and platform specifically for marketing. Its introduction in the market is an inflection point for interest in shockwave therapy for ED. This leads us to our belief that direct-to-consumer marketing is a key factor in influencing patient interest. We fully agree that it would be quite

useful to better understand the amount of money spent on advertising from GAINSwave and others but unfortunately, we are limited by the data that is publicly available.

3. We appreciate this very astute comment and agree that interest does not equate directly to dollars. We have acknowledged this in the limitations section with the below text:

Changes in text: “the study uses patient interest in these therapies as a proxy for patient use, which is a limitation. However, studies show that patients are now paying significant out-of-pocket costs for regenerative therapies, suggesting that interest is in fact translating to use.” (Lines 291-294)

In regard to the concern about the efficacy of GAINSwave, while there have been purported studies showing the efficacy of GAINSwave, or radial/unfocused shockwave therapy, these studies contain many confounding factors including small sample size and lack of blinding. Our manuscript mentions:

Changes in text: “Available efficacy data from shock wave trials exclusively analyze focused or LiSWT; there is scarce research on the effectiveness of radial wave therapy. (27,28) Despite only preliminary studies comparing acoustic and LiSWT, the two therapies have been conflated by marketing platforms.” (Lines 342-345)

4. Line 301, “authentic shockwave therapy” has been changed to “LiSWT”. We also changed “restorative” to “regenerative” at multiple points in the paper. Respectfully, we are following the terminology of the SMSNA statement, which uses both restorative and regenerative.

Reviewer B

Thank you for this interesting paper. While this concept is not new, the authors found some interesting observations. However, the hypothesis of this study is not fully investigated and the authors are required to revise this paper accordingly.

1. The title of this paper is incorrect since the data reviews other “so-called” non-restorative therapies in ED (PDE5, ICI). The authors need to change the title if they wish to discuss other ED treatment that is not regenerative in nature.

2. Significant amount of data is focused on GAINSWAVE - what about other machines? Additional information is required on the type of LIESWT and types of clinics that offer LIESWT- these are important information and can be obtained on Google analytics.

3. Information pertaining the demographics of internet users and whether there was any spike observed during key events (such as pandemics) can be valuable information for readers to appreciate the role of the internet search engines as a source of medical information.

Response B: Thank you for your comments, we sincerely appreciate the constructive comments.

1. We understand the feedback in this first comment but respectfully, we feel the focus of this

paper is the influence of direct to consumer marketing on patient interest in ED treatments. That phenomena has taken effect particularly for these “restorative” therapies. The alternatives (VED, ICI, etc) serve as a control, in a way. We hope that this explanation of the purpose elucidates why we have chosen this title.

2. We appreciate this astute comment and agree that there is significant focus on GAINSwave. This focus is secondary to the fact that GAINSwave is specifically a provider database and marketing platform. There are no other comparable marketing platforms for low-intensity targeted shockwave therapy. We are similarly interested in what types of clinics are offering these services, and have published that separately, as we feel that the scope of this study is specifically about the influence of direct to consumer marketing on patient interest. That study is now referenced in the manuscript (reference numbers 32, 33)

3. We completely agree that understanding demographics of internet users is important. Unfortunately, google trends does not track demographics of users in a manner that is publicly available, which we have stated as one of the limitations of this study. We believe that understanding how public interest has changed over COVID, when many clinics closed for an extended period and elective procedures stopped, would be a very interesting study question to pursue, but is outside the scope of this manuscript.