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There is insufficient evidence to recommend bremelanotide for hypoactive sexual desire disorder

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There is insufficient evidence to recommend bremelanotide for hypoactive sexual desire disorder

Cover Page Footnote

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INFORMED CONSENT:

There is insufficient evidence to recommend bremelanotide for hypoactive sexual desire disorder

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ABSTRACT An informed consent discussion for a patient with Hypoactive Sexual Desire Disorder.

Keywords: *hypoactive sexual desire disorder, bremelanotide*

Clinical-Social Context

Evelyn Summers [pseudonym] is a 44-year-old female who has known her current primary care doctor for 26 years. The patient has been part of the same clinical practice since childhood. The current attending physician delivered her child. She feels comfortable discussing questions related to sexual intimacy with her doctor.

Ms. Summers manages a gas station--food mart and works long hours; she considers her job stressful. She and her husband have a good relationship and there is no unusual stress in the household. Ms. Summers provides childcare for her granddaughter. She does this to help her unmarried daughter but considers this a blessing as she can watch her grandchild grow and develop.

Ms. Summers and her husband both smoke. Her husband has some shortness of breath and chronic obstructive pulmonary disease (COPD). Ms. Summers is currently trying to quit smoking. Ms. Summers has no significant medical problems and takes no chronic medications. She is minimally overweight. She has no vaginal dryness, and she has no mood disturbances.

Ms. Summers presents to the clinic stating that she would like more sexual intimacy with her husband, but "I never feel sexually aroused." She asked her doctor, "Is there any medication that can help me?" She has discussed the situation with her husband, but together they have not been able to find a solution.

Her doctor replies, "I was recently at a continuing medical education seminar and an OB/GYN specialist said there was a new medicine that has been approved by the FDA specifically for this problem. He announced to the group of doctors that the medicine can help with diminished libido and encouraged us to use it in appropriate situations.

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Why don't you schedule a return appointment in two weeks and in the meanwhile I will find out more about this medicine."

Clinical Question

How well does bremelanotide work for hypoactive sexual desire disorder?

Description of Related Literature

PubMed was queried using the search terms: "Bremelanotide AND Hypoactive Sexual Desire Disorder", with 47 results. When filtered by "Clinical Trial", 13 citations remained. Each title with abstract was reviewed. One paper was a phase 1 trial which was not reviewed further. Another paper was investigating hypertension and was considered unrelated. Two papers were on the topic of combination of sildenafil and bremelanotide for erectile dysfunction, which was also considered unrelated. Two papers were on pharmacokinetics and because they lacked Patient Oriented evidence they were not considered for review. One study was done on rats and was not reviewed. That left six papers for review.¹⁻⁶

Using the same search terms, Google Scholar was queried. This resulted in another article that was a reanalysis of data from the two Phase 3 trials by Kingsberg et. al. appraised below.⁷ This reanalysis added little new evidence. Additionally, a harsh critique of the same two trials was published and then corrected with an erratum after a spirited response by the original authors.⁸⁻¹⁰ Kingsberg, et.al. were the authors of the two Phase 3 trials which were also the most important primary clinical research articles. They concluded this spirited debate in the literature with, "The true measure of the clinical effectiveness of BMT is whether it can help patients with HSDD. This is a question that can only be addressed by a patient and her healthcare provider." Their statement seems to be an affirmation of Clinical Decision Science.

Critical Appraisals

The study by Kingsberg, et. al. is the most important paper on the topic.⁴ The researchers used a 4-week screening period, followed by a 4-week single blind, placebo only treatment period before entering a 24-week randomized, double blind placebo-controlled trial. The authors state that the single blind placebo period was to minimize the placebo effect of subjective-endpoint trials. This was followed by a 52-week open-label, optional, extension observation study. The authors did not provide Figure 1 (except in an online appendix), so it is difficult to assess the drop out in each of these phases of the study. When examining Figure 1 on the appendix, they did not differentiate between how many patients were in the active treatment versus placebo groups, making it impossible to estimate the cases of drop-out per group. This is especially important given the large differences in side effects between the two groups. Also, only 392 patients completed the study of the 614 patients that were randomized. This is a major source of bias.

The outcome variable measured was the change from baseline for the Female Sexual Function Index-desire domain (FSFI-D) and the Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO). The authors actually used only two questions from the (FSFI-D) that that were scored with a 5-point Likert scale: 1)"Over the past 4 weeks how often did you feel sexual desire or interest? [1. Almost never...5. Almost always] and 2)"Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest? [1. very low...5. very high]

For the (FSDS-DAO) the authors used only one item: "How often did you feel: Bothered by low sexual desire?

When evaluating the appropriateness of these two ordinal-level outcome measures, one must wonder why the full validated scales were not used. Also, by choosing only three questions, the variability may be less an effect of the treatment and relate more to how well the inclusion criteria were applied or the heterogeneity of the study group.

Diagnosis of hypoactive sexual desire disorder was accomplished with a screening guide by the "investigator or an appropriately licensed health care provider." This was also considered a source of bias.



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The “co-primary endpoints” showed no statistical difference, so the authors analyzed the entire scale scores to show a difference. This is of dubious appropriateness regarding research methodology.

Of note, there was a 15-25% incidence of nausea with the active treatment and less than 1% incidence of nausea in the placebo group. Similar adverse effects patterns were noted for flushing and headache.

The paper by Diamond, et. al. was a small study with eighteen cases that used a crossover design to maximize the cases measured.³ Intranasal bremelanotide was the active treatment compared to identical placebo. Patients were included if they scored <3 on the Female Sexual Function Index arousal domain (4 questions; Likert scale 0-5) and scored > 40 on the Female Sexual Distress Scale (severe symptoms). The Outcome measure was Vaginal Pulse Amplitude (VPA) using a vaginal probe while exposed to neutral or sexually explicit erotic videos. After the treatment, patients completed a study-specific questionnaire with 14 items. The investigators appropriately used a dichotomized scoring system for scoring the questionnaire. There was not a statistically significant difference in the VPA. The study reported questionnaire items individually with mixed results and the scoring was not well documented. The authors also performed voluntary patient interviews to obtain a qualitative evaluation of the patient experience. These results could not be considered conclusive.

The study by Clayton, et. al. was a Phase 2 dose finding study.² The primary endpoint used only one question from a validated psychometric. Again, this invalidates the utility of the scale by using only a component and not the complete scale. In total, the number of Satisfying Sexual Encounters (SSE) increased from a baseline to end of study by only 0.5 per month after combining the two highest doses of the study drug. The authors claim p=0.0180, but clinical meaningfulness is doubtful. The study drug had to be administered by injection and there was at least a 10% increase in adverse effects at the doses studied. This probably accounts for the 25% drop-out rate in the study population. This high loss to follow up creates a significant bias, invalidating any claims of efficacy.

The study by Koochaki, et. al. was a follow up study to the RECONNECT trials.⁵ Only 242 participants volunteered to complete a questionnaire out of 1202 original study participants. Only 80 of those completed an interview. This is a severe selection bias, making the results impossible to interpret. Although the authors report favorable responses of the study drug compared to placebo, the design of the study and the participation bias make any conclusion clinically meaningless, despite the authors' claims.

The study by Safarinejad was RETRACTED by the journal, indicating how limited the extant literature on this topic is.⁶ There is not a wide range of investigators available to compare the strength of the research methodology or the outcomes.

The report by Altop, et. al. shares a co-author (Clayton) of one of the previously reviewed papers.¹ This was an attempt to find a clinically meaningful response for a subgroup of items from previously validated psychometrics. There is no consensus of the validity of this type of analysis and in fact, it seems highly suspect. Statistical manipulation of a subjective outcome is inappropriate. There is no substitute for clinical experience in deciding clinical meaningfulness.

Using the SORT criteria, the Grade of Recommendation for not using Bremelanotide for Hypoactive Sexual Desire Disorder is B, based on few, poorly done studies.¹¹

Informed Consent

Flesch Kincaid Grade Level 5.6

“I read the medical research we talked about during your last visit. I talked with some of my colleagues. Together, we have 75 years of clinical practice experience. We all agree.

“The research studies were not well done. The medicine might help only help a tiny amount. I don’t even know what a tenth of a satisfying sexual encounter per month is. Those studies reported a lot of side effects, mostly nausea. But there could be more serious side effects in the long run.

“I’m not convinced the medicine would help you. I don’t recommend the medicine. That’s disappointing because the OB-GYN thought this would be helpful. There is not a pill or injection that will fix your problem.



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"Sexual relationships are important. But loving relationships are more important. We can explore other things you and your husband can share together."

"Why don't both you and your husband come to the next appointment. These things are difficult to talk about. I can help. I am particularly worried about miscommunication. I don't want you to lose the important things you do have together."

Relevance to Clinical Decision Science

It is common practice for Continuing Medical Education Conferences (CME) to have a content expert provide updates and recommendations for practice. For this case, the CME presenter was thought to be "enthusiastic" about new or "cutting edge" therapies. The presenter was an "early adopter" whereas the authors prefer newer therapies be tried and tested before changing clinical practice.

This report demonstrates that individual clinicians should take personal responsibility and review the evidence for recommendations prior to changing clinical practice. The larger question is how do clinicians assess the validity of evidence in a world filled with new developments in medicine. Not only do clinicians need skills in "information foraging" such as CME conferences; they must also develop and maintain critical appraisal skills.

Also, this report highlights the essential component of clinical experience for clinical decision making.¹²

This report also builds on previous publications in this journal by examining the psychometric scales or questionnaires used as outcome measures for clinical research.¹³ Although purported to be clinically meaningful, the authors are experienced clinicians and disagreed with the clinical researchers after personally reviewing the outcome measures and questionnaires. This is where the clinician's experience is critical to evaluate the clinical relevance and meaning for an individual patient of these subjective outcome measures.

Conflict of Interest Statement

None of the authors declare any conflict of interest for this manuscript.

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