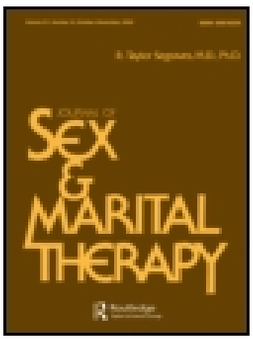

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Challenges in designing psychological treatment studies for sexual dysfunction

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With the availability of the first ever medication (flibanserin) approved by the U.S. Food and Drug Administration (FDA) in 2015 for the treatment of low desire in premenopausal women, many clinicians and researchers have become interested in the question of efficacy of other forms of treatment. The finding that flibanserin improves sexually satisfying events by only 0.5 - 1 per month (Gao, Yang, Yu, & Cui, 2015; Jaspers et al., 2016) illustrates that the drug is not a panacea and that other treatment options are needed. Non-pharmacological treatments may be particularly appropriate for women who have significant psychological and/or dyadic contributors to their low desire, or simply cannot take flibanserin due to its serious interactions with alcohol and medications such as CYP3A4 inhibitors or other chronic medical conditions such as hepatic impairment. Moreover, flibanserin's road to approval was not straightforward, and it was rejected by the FDA twice before its eventual approval. The fact that it was approved only for premenopausal women with HSDD raises another issue in that even with its modest efficacy, it is only benefiting a proportion of the population of women who experience sexual concerns, and its long-term efficacy is essentially unknown. The goal of this Brief Communication is to explore the efficacy of psychological treatments for low desire in women and to consider methodological limitations inherent to carrying out psychological treatment outcome research. We end with some specific suggestions for researchers to consider as they design future psychological trials for low desire.

Pyke and Clayton (2015) provided a thoughtful critique of available controlled outcome studies focused on the treatment of women with low sexual desire (namely, hypoactive sexual desire

disorder; HSDD).[1] Using the standards set by the FDA for pharmacological trials, Pyke and Clayton concluded that "clinical trials of psychological treatments for sexual dysfunction should be held to the same standards of evidence as for clinical trials of medications" (p. 2451). The 10 standards included: (1) clear goals, (2) sufficient information on the therapy to duplicate it, (3) randomization to treatments, (4) equality of treatment groups, (5) adequate controls, (6) measure of compliance, (7) employ validated measures, (8) demonstrate clinical relevance, (9) clinically relevant duration, and (10) positive benefit-risk ratio. As noted by McCabe and Connaughton (2015) in their accompanying editorial, the paper by Pyke and Clayton (2015) provides a good point of discussion for future psychological treatment outcome studies in sexual dysfunction (for women and men); however, we believe that a number of the conclusions reached in this paper are not sufficiently supported by existing research, and/or do not advance our knowledge of effective treatments for sexual dysfunction. We hope that our remarks will continue the dialogue among clinicians and researchers to attain the highest possible standards, within what is achievable, when designing psychological treatment outcome studies. Our comments are organized around three assumptions that we believe underlie Pyke and Clayton's (2015) conclusions regarding the efficacy of psychological treatments for HSDD.

Assumption #1: Psychological treatments for HSDD in women are not effective

The standard approach to evaluating efficacy (i.e., improves relevant outcomes to a greater degree than a relevant control condition in a tightly controlled study to maximize internal

[1] Of note, the reviewed literature and critique by Pyke and Clayton (2015) focus on the diagnosis of HSDD (DSM-IV-TR, American Psychiatric Association, 2000). As far as we are aware, there has been no published studies on psychological or pharmacological treatment of the new DSM-5 (American Psychiatric Association, 2013) condition, Female Sexual Interest/Arousal Disorder (FSIAD).

validity) and effectiveness (i.e., improves relevant outcomes in a study utilizing more heterogeneous samples being treated in real-world circumstances, maximizing external validity) of a therapeutic intervention, in psychology and medicine, is to conduct a quantitative review and, if possible, a meta-analysis, as in the widely-used Cochrane reviews. Frühauf and colleagues (2013) conducted a systematic review and meta-analysis to quantify the efficacy of psychological interventions for sexual dysfunction. Only four studies evaluating psychological treatments for HSDD were identified, and none of these studies reported on the use of a manualized treatment. Nonetheless, Frühauf et al. (2013) found a large effect size for psychological treatments for HSDD (d = 0.91; 95% CI: 0.38 to 1.45; p = .012; n = 4; I^2 = 0.0%), and they concluded, "Psychological interventions have large effects on symptom severity in women with Hypoactive Sexual Desire Disorder" (p. 926). This meta-analysis also found that effect sizes for the increases in sexual satisfaction and reductions in symptom severity for treatment of HSDD using cognitive-behavioral therapy (CBT) and CBT plus skills training, were in the moderate to large effect size range, as compared to a wait-list control (Frühauf et al., 2013).

Though the findings of this meta-analysis challenge the conclusions by Pyke and Clayton (2015) that "it does not appear that any published trials provide fully sound proof that psychological treatments are effective for HSDD, whether CBT, or mindfulness training" (p. 2457), it is important to note that several of the ten standards listed earlier for conducting clinical trials in sexual medicine were not met by the studies included in the meta-analysis by Frühauf and colleagues.

On the basis of the Frühauf meta-analysis, and another systematic review (Günzler & Berner, 2012), neither of which were cited in the Pyke & Clayton (2015) critique, the International Consultation on Sexual Medicine, Committee on Psychological and Interpersonal Dimensions of Sexual function and Dysfunction recommended that clinicians consider CBT in the treatment of women with low sexual desire with a Grade A recommendation i.e., a strong recommendation based on high quality evidence (Brotto et al., 2016). We believe that these reviews demonstrating the efficacy of CBT for HSDD should not be taken as "proof", or rather in this case lack of proof, for the therapy's benefit. Claims such as "it does not appear that any published trials provide fully sound proof that psychological treatments are effective for HSDD" (Pyke & Clayton, 2015, p. 2457) perpetuate problematic notions that lack of "proof" equates to weak evidence for efficacy. A demonstration of "proof" is impossible in science because evidence, not proof, is the standard by which hypotheses are evaluated using the scientific method.

Assumption #2: The psychological treatment outcome literature for HSDD is flawed because of the lack of adequate controls.

Pyke and Clayton (2015) criticized outcome studies of mindfulness-based therapy for sexual dysfunction on the basis that the studies did not include an adequate control group, but rather employed a wait-list control group (Brotto & Basson, 2014; Brotto et al., 2012). Different types of control groups may be implemented in treatment trials; namely, an active control group would represent an already established treatment as the comparison arm, whereas a placebo control group is not designed to elicit any treatment effects, but instead, to control for the "placebo effect"-- the belief by the individual that the treatment works. Designs with an active control arm

often constitute non-inferiority studies in which the hypothesis is that the experimental treatment is not inferior (i.e., just as good as) the active control therapy. A placebo controlled study, on the other hand, is designed to demonstrate that the experimental treatment (usually a medication) is superior to the placebo group.

Pyke and Clayton (2015) are not the first to criticize randomized controlled trials (RCTs) of psychological interventions. In 2001 (Chambless & Ollendick, 2001) and in 2004 (Westen, Novotny, & Thompson-Brenner, 2004), experts in psychological clinical trials designs, recognized the difficulty of designing a "placebo-like" control, the impossibility of maintaining double-blind conditions, the challenge of standardizing interventions, the importance of the therapist-patient fit, and the reduced external validity of psychotherapy in the context of RCTs on psychological treatments. The challenge in using a wait-list control group versus active control group is that the former may not allow for the testing of non-specific factors, such as normalization of one's experience, social support, education, and basic coping skills (though we acknowledge that even the assessment process leading to participation in a research trial may be experienced as therapeutic by some individuals). A wait-list control group simply controls for the passage of time, as well as possibly expectations that improvement might occur if participants are in a delayed treatment arm. Pyke and Clayton (2015) suggested that supportive psychotherapy could be considered as an appropriate control and that this would provide the same duration of contact with the therapist as in the active treatment arm. Though we agree that comparison to supportive psychotherapy would be interesting, it must be noted that this would not constitute a placebo control group, but rather an active control group because it elicits several of the factors that contribute to improvements that are not specific to the treatment itself. As an

example, one published randomized trial of CBT (as the experimental arm) versus supportive group therapy (as the active control arm) for women with vulvodynia showed similar improvements in pain severity, depressive symptoms, and anxiety, with the CBT group showing significantly greater satisfaction with treatment, presumably due to the skills-based nature of that group (Masheb, Kerns, Lozano, Minkin, & Richman, 2009). One might conclude from this study that supportive psychotherapy did not only elicit therapy non-specific effects, but rather, was the supportive element, itself, was efficacious. Though Pyke and Clayton (2015) attempt to make a case for supportive psychotherapy as an adequate active control group, we believe its benefits to extend beyond its ability to elicit only nonspecific benefits.

So if supportive psychotherapy has more "treatment ingredients" than simply non-specific therapeutic ingredients, what, then, would an active control group in a psychological treatment outcome study entail? Pyke and Clayton (2015) suggested that routine primary care could also be considered as an active control group. In reality, however, routine primary care is typically no care. Numerous studies have shown that primary care physicians rarely address sexual functioning in women (Goldstein, Lines, Pyke, & Scheld, 2009) and most report little confidence in even making a diagnosis of HSDD (Harsh, McGarvey, & Clayton, 2008), even in more specialized populations such as survivors of cancer (Bober, Carter, & Falk, 2013). It is doubtful that routine primary care would have the ability to invoke the nonspecific benefits of a therapeutic intervention when issues regarding sexual concerns are typically not discussed or addressed in this context.

If we consider the placebo group in a 2-arm pharmacological trial, participants have the belief that the medication they are receiving has a 50% likelihood of being active treatment. The

placebo response elicited reflects participants' expectations about treatment, the support and validation from the study team members, and apparent "side effects" from the placebo; these side effects may be due to increased attunement to body sensations as the participant becomes hypervigilant about drug side-effects.

Furthermore, in drug trials, participants' involvement is limited to following dosage instructions. Participants in drug trials may be aware that they are in a placebo control arm if they do not experience any of the side effects that are detailed in study information sheets. In contrast, in psychological studies study participant information sheets will identify the names of the two types of treatment and, upon randomization, participants know which treatment group they have been assigned to. As the psychological therapy progresses, their knowledge of what treatment is being administered also increases and their participation is active and under their control. We would argue that these very basic differences between medication and psychological treatment placebo groups preclude the possibility of identical standards of evidence. Because RCTs are accepted to be the optimal means of establishing efficacy in psychotherapy (Chambless & Ollendick, 2001), other research designs in psychological efficacy studies incorporating different comparison groups may need to be employed. We expand on this further under Assumption #3.

We struggle to identify what would constitute a placebo group within a psychological treatment trial for women's low desire, and as a result, we believe that standard #5 (adequate controls) may not be attainable. However, we welcome feedback from experts on defining such a placebo control group that might be implemented.

Assumption #3: Psychological treatment efficacy can be directly compared to medication efficacy.

Pyke and Clayton (2015) made a comparison between the efficacy of pharmaceutical interventions, CBT, and mindfulness therapy for female sexual desire and arousal disorders. Though not stated explicitly, the organization of their Discussion makes the case for a possible hierarchy of efficacy, with medication exhibiting the strongest evidence for efficacy/effectiveness followed by CBT, with mindfulness ranked third. We maintain that these are not valid comparisons, as there are no data on effectiveness of pharmaceutical treatment of low desire in women i.e., application of the treatment under typical 'real life' conditions as opposed to the efficacy obtained from strictly controlled clinical trials with extensive exclusion criteria for participants. More importantly, we are not aware of a single study that has directly compared a psychological versus a pharmacological treatment for HSDD (the closest comparison was a study of Ginkgo Biloba extract which was evaluated against psychological therapy in women with sexual arousal disorder; Meston, Rellini, & Telch, 2008).

In the clinical psychology literature, many studies have compared the relative efficacy of medication and psychotherapy, and combinations thereof, for a variety of psychological disorders. In general, these comparisons are difficult to make, even in the context of well-planned RCTs. For example, the Treatment of Depression Collaborative Research Program (Elkin, Parloff, Hadley, & Autry, 1985) was an ambitious attempt to compare the efficacy of psychotherapy and medications for the treatment of depression. The initial results of the study suggested superiority of medication over CBT in the treatment of severe depression. However, further exploration of the results suggested that differences regarding the competence of

implementing treatments across sites may account for these results. Indeed, most studies have found that CBT in particular is at least as efficacious, if not more so, compared to pharmaceutical interventions or combination therapies, with better maintenance of treatment gains for a wide variety of mental health conditions (Barlow, Gorman, Shear, & Woods, 2000; Butler et al., 2006; Dimidjian et al., 2006).

High-quality studies directly comparing CBT and mindfulness interventions are only beginning to be published, but the initial research generally suggest similar efficacy for both types of interventions (Arch et al., 2013; Khoury et al., 2013). Clearly, high-quality comparisons with multiple replications are needed to draw strong conclusions regarding relative efficacy of interventions. The currently available literature suggests that empirically-supported psychotherapies are at least as efficacious as medications in treating many psychological disorders, and that mindfulness-based therapies may be as efficacious as CBT. While it is possible that this pattern would be different in the case of psychological treatment of sexual dysfunction, there is currently little evidence that this is the case. Instead of focusing on which treatment is better, however, perhaps the more relevant research question is which treatment is best for whom. As we gather more evidence supporting a variety of approaches to treatments for desire and arousal difficulties, it is important to keep in mind the individual differences that may influence the likelihood of a particular treatment demonstrating clinical benefit.

Other considerations for researchers evaluating psychological treatments for low desire in women

There are several characteristics of psychological treatment studies of sexual dysfunction that complicate the outcome literature and that make direct comparison between the efficacy of

different treatments challenging. First, almost every trial of CBT for sexual dysfunction cited by Pyke and Clayton (2015) (Hucker & McCabe, 2015; Jones & McCabe, 2011; McCabe, 2001; Trudel et al., 2001) was either explicitly a couples-based treatment, or included a current relational partner in some aspect of therapy. In contrast, a majority of the mindfulness trials critiqued by Pyke and Clayton did not include partners in treatment (e.g., Brotto, Basson, & Luria, 2008), and most did not even require participants to be involved in a current romantic relationship (e.g., Brotto & Basson 2014). Individuals seeking treatment for sexual dysfunction without a current partner may differ in important ways from those with a current partner (Catalan, Hawton, & Day, 1991). Furthermore, the quality of the relational context is an important predictor of distress regarding sexual impairment (Bancroft, Loftus, & Long, 2003). As such, interventions that include partners working to improve communication and relationship satisfaction may be more efficacious regardless of the specific treatment technique. At a minimum, we urge researchers to consider the impact of partner-related components and outcomes in their study designs.

Second, almost every trial of mindfulness for sexual dysfunction to date has utilized treatment protocols that also include components of CBT, such as cognitive restructuring. Comparison of studies utilizing "pure" CBT protocols and those that utilize treatments that combine mindfulness with CBT do not allow for a determination of relative efficacy of CBT vs. mindfulness. Indeed, we are aware of only one small trial that explicitly compared "pure" mindfulness (without cognitive restructuring) to CBT for sexual dysfunction. In this study, both treatment modalities produced similar levels of improvement in sex-related distress (Brotto, Seal, & Rellini, 2012).

Third, a factor seldom considered in the context of treatment efficacy is how well women might tolerate the different treatments. Even if CBT or mindfulness are established as less effective than medications, these psychological approaches may be better tolerated given that they have not typically been associated with side effects such as those caused by some medications to treat low sexual desire in women (Jaspers et al., 2016). Because low sexual desire is not a fatal condition, it is likely that the risk-benefit ratio and the side-effect profile of a medication may be key in determining patient adherence. Mindfulness is likely associated only with positive side effects, such as improved communication between partners and better conflict resolution (Carson, Carson, Kim, & Baucom, 2004; Hucker & McCabe, 2014; Laurent, Hertz, Nelson, & Laurent, 2016). While CBT is effective for a wide range of conditions, there is often a large drop-out rate (Imel, Laska, Jakupcak, & Simpson, 2013). Mindfulness treatment studies often show very low rates of drop out, and participants report continuing to practice their acquired skills in the long-term (Baer, 2003). Thus, while intent to treat analyses are needed, these may show that mindfulness results in equivalent total benefits because a higher percentage of patients are willing to remain in treatment and to continue implementing skills post-treatment. Because women continue to be sexual well into the elderly years, it is likely that learned psychological skills can continue to be "put to practice" whereas medications, even if efficacious, may not result in long-term behavioral changes, and their long-term safey remains unknown at the present.

We sincerely hope that future direct comparisons of interventions will shed more light on possible differences in efficacy. However, even for treatments in areas with much more research activity, such as anxiety and mood disorders, it has proven quite difficult to make these direct

comparisons. One example of this difficulty is the recent literature attempting to answer the question of whether CBT is more effective that non-CBT therapies in the treatment of anxiety and mood disorders.

Specifically, Tolin (2010) conducted a meta-analysis utilizing RCTs making direct comparisons between CBT and "*bona fide"* alternative therapies (e.g., psychoanalysis, client-centered therapy). He found that, across 26 studies, CBT resulted in slightly better outcomes on measures of primary symptom severity. In response, Baardseth and colleagues (2013), conducted a "counter" meta-analysis in which they expanded the number of included studies and re-classified treatments based on responses from psychologists (primarily practitioners). They found no significant differences in effect sizes between CBT and other forms of therapy. In response, Tolin (2014) re-ran his initial analyses, adding studies included by Baardseth and colleagues to explore reasons for the conflicting results. Tolin noted a number of likely reasons for the differing results, including the fact that Baardseth combined different types of analyses (e.g., completer and intent-to-treat), included multiple measures of different constructs, and utilized studies with questionable methodological quality (e.g., those without assessors blind to experimental condition). As noted by Tolin, all of these methodological and statistical issues increase the amount of error variance in analyses, making the detection of true effects less likely. Thus, without great care and nuanced understanding of the research tools being employed, pre-existing beliefs of researchers can easily color the results of even powerful methods like meta-analysis.

Suggestions for moving the science of treatment efficacy for women's low desire forward

We fully agree with Pyke and Clayton's (2015) views that the reporting of RCTs in social and psychological interventions can be improved upon; thus, in the United Kingdom (UK) and Canada, efforts are underway to develop the CONSORT-SPI: A CONSORT[2] Extension for Social and Psychological Intervention (Mayo-Wilson et al., 2013). Other quality assessment guidelines for psychological treatment studies have been developed, such as the report by the Centre for Reviews and Dissemination (Khan, ter Riet, Popay, Nixon, & Kleijnen, 2001) which is intended as a general method for assessing both medical and psychosocial interventions. In the UK, it has been recognized that adverse event reporting in psychological intervention trials has been given less attention; recommendations for the future practice of recording and reporting of adverse events have been made to bring these types of trials in line with drug trial reporting (Duggan, Parry, McMurran, Davidson, & Dennis, 2015).

When comparing the efficacy of different interventions for sexual dysfunction, we hope that researchers will utilize these lessons gained from past attempts in other areas, such as those of Tolin (2010) discussed above, to compare interventions. Specifically, any legitimate comparisons of different treatments should take care to correctly categorize interventions (e.g., as CBT vs. mindfulness vs. combined treatments), account for study quality, and generally minimize error variance to allow for detection of true effects. Furthermore, we must consider that direct comparisons of different treatments may tell us more about relative efficacy rather than represent an exact replication of the study designs used in medication RCTs.

Conclusion

[2] Consolidated Standards of Reporting Trials

Pyke and Clayton (2015) as well as McCabe and Connaughton (2015) made a number of excellent points regarding the need for more trials of psychotherapeutic treatments for female sexual desire and arousal problems. We fully support their recommendation that researchers include more information on responder and remittance rates, and that more consistent reporting of results from trials is needed. In our view, however, attempts to compare the efficacy of medications, CBT, and mindfulness at this time are premature, particularly given there have been no direct comparisons of psychological and pharmacological treatments for low sexual desire in women. Going forward we recommend a concerted effort to obtain adequate funding for psychological treatment trials that are methodological rigorous, contain control groups appropriate for psychological interventions, are generalizable and feasible, attend to partner-related factors, and are free of commercial bias.

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