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Which Emperor Has New Clothes? Biology Versus Psychology in the Era of Statistical Magic

Richard Balon

Departments of Psychiatry and Behavioral Neurosciences and Anesthesiology, Wayne State University, Detroit, Michigan, USA

Robert Taylor Segraves

Department of Psychiatry, Case Western Reserve University, Cleveland, Ohio, USA

At first glance, the article by Brotto, Basson, et al. (2017) may appear to be just zealous advocacy by one group of mental health professionals for their preferred treatment model for female hypoactive sexual desire disorder (HSDD): psychological interventions. It was written in response to an article by Pyke and Clayton (2015), who have been actively involved in investigating pharmacological intervention for this disorder. The article by Pyke and Clayton (2015) insists that pharmacological and psychological interventions be held to the same standards of scientific rigor and concluded that the evidence for psychotherapeutic interventions is remiss. Pyke and Clayton (2015) write that, "All successful trials should meet 10 precepts: (i) clear goals; (ii) sufficient information on the therapy to duplicate it; (iii) randomization to treatments; (iv) equality of treatment groups; (v) adequate controls; (vi) measure compliance; (vii) employ validated measures; (viii) demonstrate clinical relevance; (ix) clinically relevant duration; and (x) positive benefit-risk ratio. Though these are important requirements, to fulfill them all is certainly a tall order. Pyke and Clayton (2015) add that, "For incorporation into practice, any new treatment should meet four more standards: (i) statistically significant superiority; (ii) clinically significant superiority; (iii) independently reproduced; and (iv) generalizability, that entry criteria would apply to symptomatically complex patients, and that a treatment is applicable to provide benefit in a broad target population" (p. 2451). Another tall order. After analyzing five controlled trials (three CBT and two mindfulness meditation training), Pyke and Clayton (2015) conclude that psychological treatments for HSDD are not yet supported by adequate clinical trials and presented a requirement that current scientific and regulatory standards for drug treatment trials should also be applicable to psychological treatment trials.

In their response, Brotto, Basson, and colleagues (2017) address several points or, as they call them, assumptions, raised by Pyke and Clayton (2015), such as that psychological treatments for HSDD in women are not effective; that the psychological treatment outcome literature for HSDD is flawed because of the lack of adequate controls; and that psychological treatment efficacy can be directly compared to medication efficacy. As expected, they present their evidence that

Address correspondence to Richard Balon, Department of Psychiatry, Tolan Park Building, 3rd floor, 3901 Chrysler Service Dr., Detroit, MI 48201, USA. E-mail: rbalon@wayne.edu

psychological treatments are effective for HSDD in women, citing the International Consultation of Sexual Medicine consensus (see Brotto, Atallah, et al., 2016); that the requirement of adequate controls may not be attainable; and that the literature suggests that empirically supported psychotherapies are at least as efficacious as medications in treating many psychological disorders. Brotto, Basson, and colleagues could not and did not present such evidence for the HSDD. They also used the term *psychological disorders*, which has etiological, yet not always proven, explanations and connotations.

Reading of these two articles may leave the reader a bit confused, as it reiterates the old biology versus psychology discussion and guild conflicts at just another level.

The article by Brotto, Basson, and colleagues (2017), however, transcends professional parochialism and addresses important points that will need to be considered in evaluating clinical trials of psychotherapies for sexual disorders and in evaluating all trials in this area.

The first point is that although all clinical trials should be held to the same scientific standards, different control groups may be required for each type of intervention. An inert placebo may be a logical control group for a pharmacological trial. In fact, such a condition may be necessary in any comparison of pharmacological and psychological interventions to be certain that the drug condition was effective in the studies population. The appropriate control for a psychological intervention is less clear. It is virtually impossible to conceive of a psychotherapy control that is both plausible and double blind. The next logical option is a control group of "supportive psychotherapy." However, supportive psychotherapy is not an inert intervention. It is not always clear what investigators mean by "supportive psychotherapy"; it is not always well defined, mixes various rudimentary psychological interventions, and is not manualized. According to some, its goal is strengthening the ego defenses. In practice, the investigator elicits a history, explores a differential diagnosis, examines relationship issues, provides an explanation (diagnosis), and validates the complaint. Indeed, some studies have not found significant differences between supportive therapy and more defined psychological interventions. This may attest to the importance of normalization of experience, social support, education about relationships, creation of a strong therapeutic relationship (the strongest ingredient in most, if not all, therapies), and other nonspecific factors offered by expert clinicians. The logical conclusion is that a waiting list may be the best control for a psychological intervention trial. Thus the control for a psychotherapeutic intervention may need to be quite different from that of a pharmacological intervention. Another reflection on this point is the incredible power of nonspecific interventions both in psychotherapy and pharmacological trials that are not reflected in most, if not all, clinical trials (for a thorough discussion, see Kramer, 2016). As Kramer (2016, p. 113) writes, our controlled trials, conventionally analyzed, may not reflect the reality of clinical practice. One can also ponder if the extra effort spent on learning specific psychological interventions is necessary, given the power of nonspecific interventions in supportive psychotherapy.

Another major issue raised by Brotto, Basson, and her colleagues (2017) is a recommendation to shift the research question from which type of intervention is better in general to which type of intervention is best for which group of patients in particular. From our perspective, this is a more responsible approach. One would expect transient or situation-specific problems to be more responsive to psychological interventions and more global, persistent problems to be more responsive to pharmacological interventions. These commonly held assumptions are subject to investigation. The publication by Brotto, Basson, et al. (2017) may facilitate this area of inquiry.

Clinicians could utilize clear guidance in dealing with specific situations or patients rather than brooding over statistical significance.

The irony in this exchange is that the efficacy of the only approved product to treat HSDD in women in the United States is clearly limited. This product, flibanserin, is indicated for acquired generalized HSDD in premenopausal women. Flibanserin was originally developed by Boehringer-Ingelheim as an antidepressant. However, it failed as an antidepressant in clinical trials. A questionnaire (ASEX, McGahuey and colleagues, 2000) used to identify sexual side effects in these trials appeared to suggest a positive effect on sexual function. Thus, Boehringer-Ingelheim developed flibanserin for HSDD, interestingly only in women. After approval of this compound was denied by the U.S. Food and Drug Administration (FDA), Boehringer-Ingelheim sold this compound to Sprout Pharmaceuticals, which mobilized considerable political pressure from women's groups to demand the FDA to approve this product. Flibanserin was approved on the third attempt (interestingly with no additional efficacy data, just with added safety data, on August 18, 2015). Shortly after its approval, the compound was sold to Valeant Pharmaceuticals. Its sales have been disappointing so far—only 1,841 prescription were filled in the first week. This could be attributed to its limited efficacy and high price, but also to the fact that Sprout Pharmaceuticals pledged not to engage in any consumer advertising for 18 months.

The evidence of flibanserin efficacy for the FDA approval was established in three 24-week randomized, double-blind, placebo controlled trials (Derogatis et al., 2012; Katz et al., 2013; Thorp et al., 2012). In all trials, flibanserin performed statistically better on various measures. However, some would question clinical superiority of some differences. At the beginning, we mentioned the recommendations by Pyke and Clayton (2015), such as clinical significance and generalizability. Is one-half additional satisfying sexual events per month clinically significant? Are the results truly generalizable to all women? On the other hand, the evidence for psychological interventions is limited to a handful of studies. As Brotto, Basson, and colleagues note, only four studies were identified for a systematic review by Fruhauf, Gerher, Schmidt, Munder, & Barth (2013), and Pyke and Clayton (2015) cite only five studies (both articles use the same two CBT studies and differ in other studies in their analysis) examining the psychological treatment modalities in HSDD. These studies include a small number of subjects, differ in therapy modalities, are usually not manualized, and do not necessarily include measures of clinical significance. Thus, it seems from glancing over the treatment studies in the area of female HSDD that neither the only approved medication for this indication, flibanserin, nor the psychological modalities fulfill the four major requirements of Pyke and Clayton (2015): statistical superiority, clinical superiority, reproducibility, and generalizability.

Frequently, meta-analysis of existing studies (at times, with added available data) is used to summarize and analyze all available data about a drug or other subjects of study to provide a clearer picture of all available findings. So far, there are two meta-analyses and systematic reviews of the efficacy and safety of flibanserin. Using a total of 3,414 patients, Gao, Yang, Yu, & Cui (2015) found flibanserin more effective than placebo and thus an effective and safe treatment for HSDD, although they mention that the drug effect was modest—about 10% better than placebo in the data presented for the FDA approval. On the other hand, Jaspers and colleagues (2016), including 5,914 women, reported that flibanserin, on average, resulted in one-half additional satisfying sexual events per month while statistically and clinically significantly increasing the risk of dizziness, somnolence, nausea, and fatigue. Can anything be clearly concluded from these meta-analyses? Or are we witnessing what Alvan Feinstein (1995) called the statistical alchemy

for the 21st century? Feinstein (1995) made the comparison to alchemy as "the idea of getting something for nothing, while simultaneously ignoring established scientific principles, produces an immediate analogy to the alchemy. . . . An advantage of alchemy was a principle that might be called the *free lunch*; the alchemist hoped to convert existing things to something better, such as changing base metals into gold. A scientific disadvantage of alchemy might be called the *mixed salad* principle. Before the reproducible precision of modern chemistry, the alchemists worked with substances that were heterogenous, poorly identified mixtures. . . . The free lunch and mixed-salad principles are the reason why meta-analysis is analogous to statistical alchemy for the 21st century" (p. 71). Feinstein (1995) does not discard meta-analysis, but complains that "the meta-analysis of randomized trials concentrates on a part of the scientific domain that is already well lit, while ignoring the much larger domain that lies either in darkness or in deceptive glitters" (p. 78). Fruhauf and colleagues' (2013) meta-analysis of psychological treatment modalities seems to have some of the issues suggested by Feinstein (1995)—such as using a heterogenous mixture of only four studies in the case of HSDD.

One might surmise that the critical issue is conflict of interest for one's preferred and licensed intervention. Conflict of interest beyond the usually cited financial conflict of interest is a reality of the modern world and science. Some have written of confluence of interest (Cappola & FitzGerald, 2015), pointing toward bias and conflict of interest beyond the pharma money, such as the influence of departments, research institutions, universities, other sponsors, journals, and, we would add, *ideology*. One might also surmise that both sides of this discussion entertain not only different views of what efficacy and effectiveness are, but also different astute clinical observations, which, as Kramer (2016) in his book on antidepressants emphasizes, go far more beyond what scales and other measures tell us (e.g., in his clinical observation, antidepressants can be restorative, making depressed patients more available emotionally and more engaged in various activities—those are issues not captured on scales, yet important in clinical practice). Only future work may help us to answer these questions.

Well, it seems that both emperors have new clothes, though of different quality. But what would the child in the Hans Christian Andersen tale say?

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