THE PHARMACEUTICALIZATION OF PREMENSTRUAL SYNDROME

FROM PROGESTERONE TO SARAFEM® (FLUOXETINE)

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1. Introduction: what's PMS and PMDD

PMS

- Premenstrual syndrome
- certain environmental, metabolic, or behavioral factors that occur during the luteal phase of the menstrual cycle… leads to cyclic emotional, physical, or behavioral symptoms that interfere with an individual's lifestyle (International Classification of Diseases-11, or ICD-11)
- usually starting four to five days before menstruations and ending within four days after the period begins; at least three menstrual cycles in a row
- More than 150 different changes documented (Chrisler and Caplan, 2002)

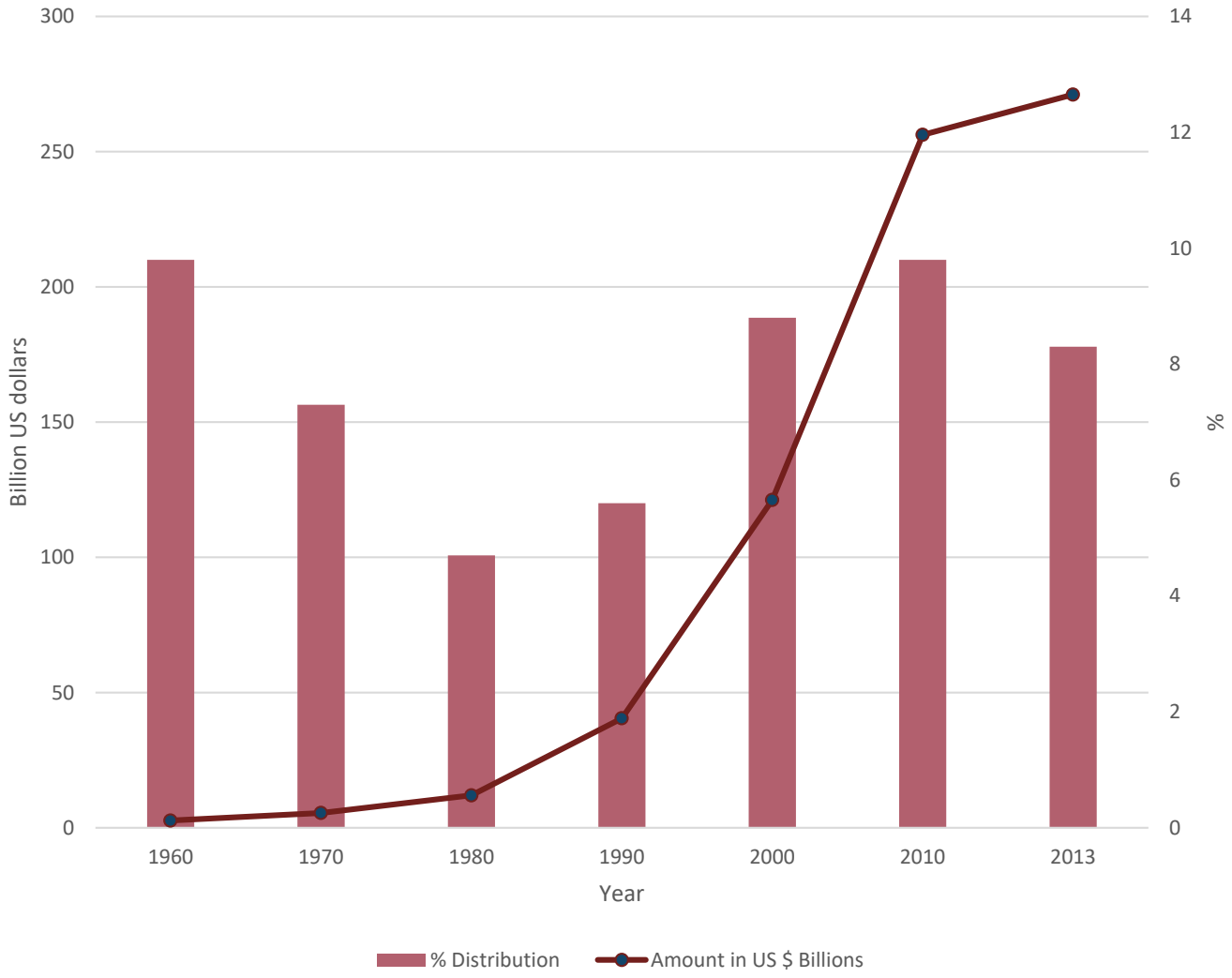
PMDD

- Premenstrual dysphoric disorder
- severe and disabling form of PMS with mood symptoms being dominant.
- depressive disorder.
- While PMS still had no precise definition, the prominence of mood disturbances attracted much attention in the mental health field.

Prescription Drugs Expenditure for 1960-2013

reproduced from Scott (2016)

Fig. 1: National Health Expenditures on retail outlets sales of prescriptions drugs for 1960-2013, by Aggregate Amount and Percent Distribution



Contoso

1. Introduction: what are pharmaceuticalization and medicalization?

Pharmaceuticalization

Pharmaceuticalization refers to "the process by which social, behavioural or bodily 'conditions' are treated or deemed to be in need of treatment, with medical drugs by doctors (or patients)." (Abraham, 2010)

Medicalization

Medicalization is a process in which "a problem is defined in medical terms, described using medical language, understood through the adoption of a medical framework, or 'treated' with a medical intervention." (Conrad, 2007)

Q1. Relationships?

Q2. Historical context → changing characteristics.

“Treatment with a progestogen is almost invariably successful…with less labour for the patient, by the implantation of progesterone, which remains effective for many months.” (Dalton, 1954)

General practitioner Katharina Dalton (1916-2004) coined the term “premenstrual syndrome”.

“Trauma in women heals quicker than in men because women have progesterone, particularly menstruating women…if you give women natural progesterone – and menstruating women have natural progesterone - within 14 days of a severe accident, they heal up much quicker than a man with severe trauma.” (Dalton, 1999)

“PMS Guru” Katharina Dalton (1916-2004) coined the term “premenstrual syndrome”.

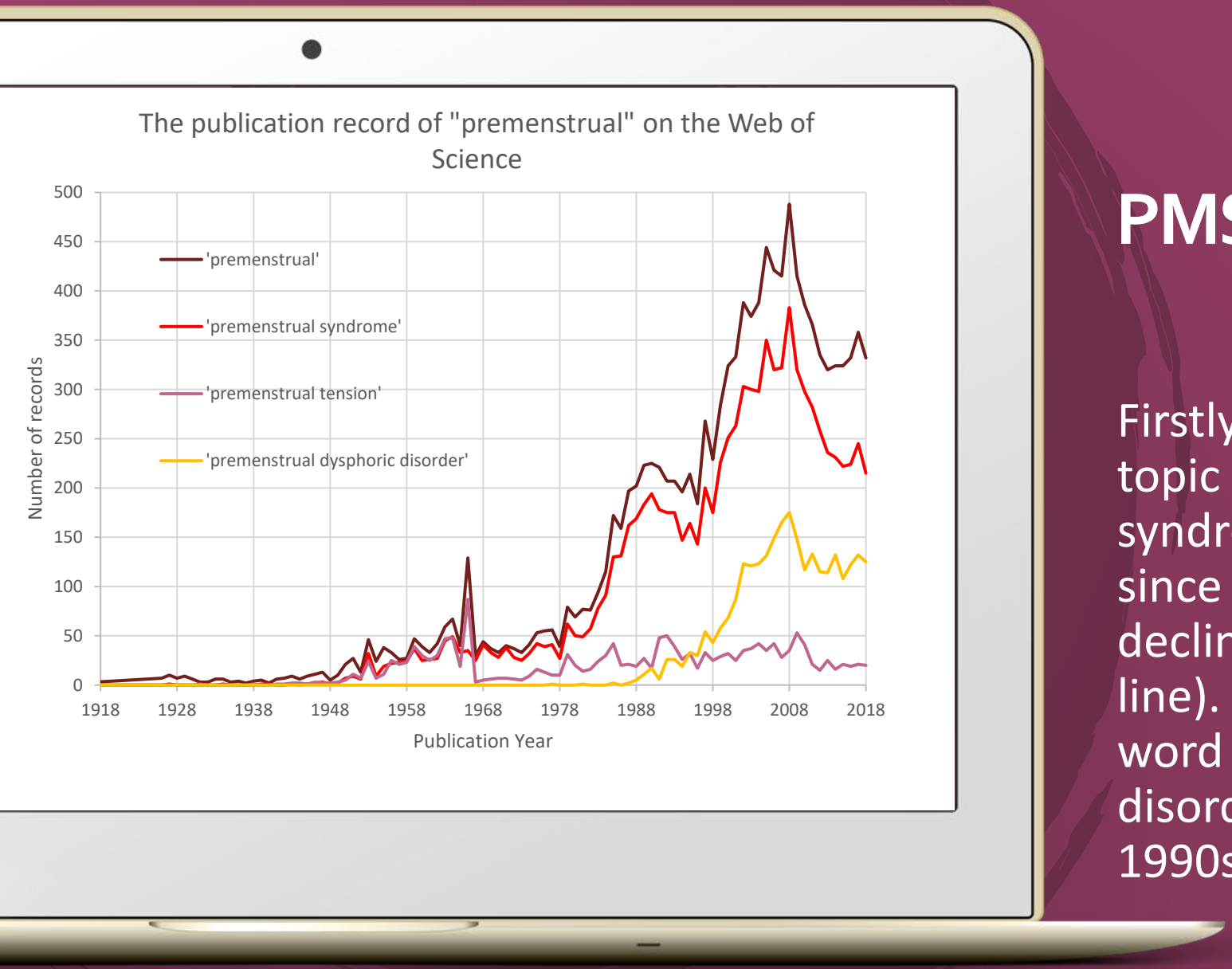
Critiques from scholarly peers

A Weakly Supported Scientific Theory: Progesterone

"Katharina Dalton is forceful in her claims for the value of progesterone as a therapeutic agent but in this book she has not produced nearly enough evidence to support her view, and this is the more tragic because it represents almost 25 years of research work in this one aspect of gynaecology." (Lloyd, 1978)

"Unfortunately, I failed to persuade her against the use of progesterone as a 'therapy' for premenstrual symptoms. Dalton's belief that only synthetic progesterone caused side-effects has achieved 'cult' status…" (Grant, 2004)

"Her work has been largely anecdotal." (Dan and Lewis, 1992)



PMS and PMDD becoming hot research topics

Firstly, a large amount of papers with topic word of ‘premenstrual syndrome’ is produced each year since 1980s but it seems to be declining in the last ten years (the red line). Secondly, research with topic word of ‘premenstrual dysphoric disorder’ began to accumulate since 1990s (the orange line).

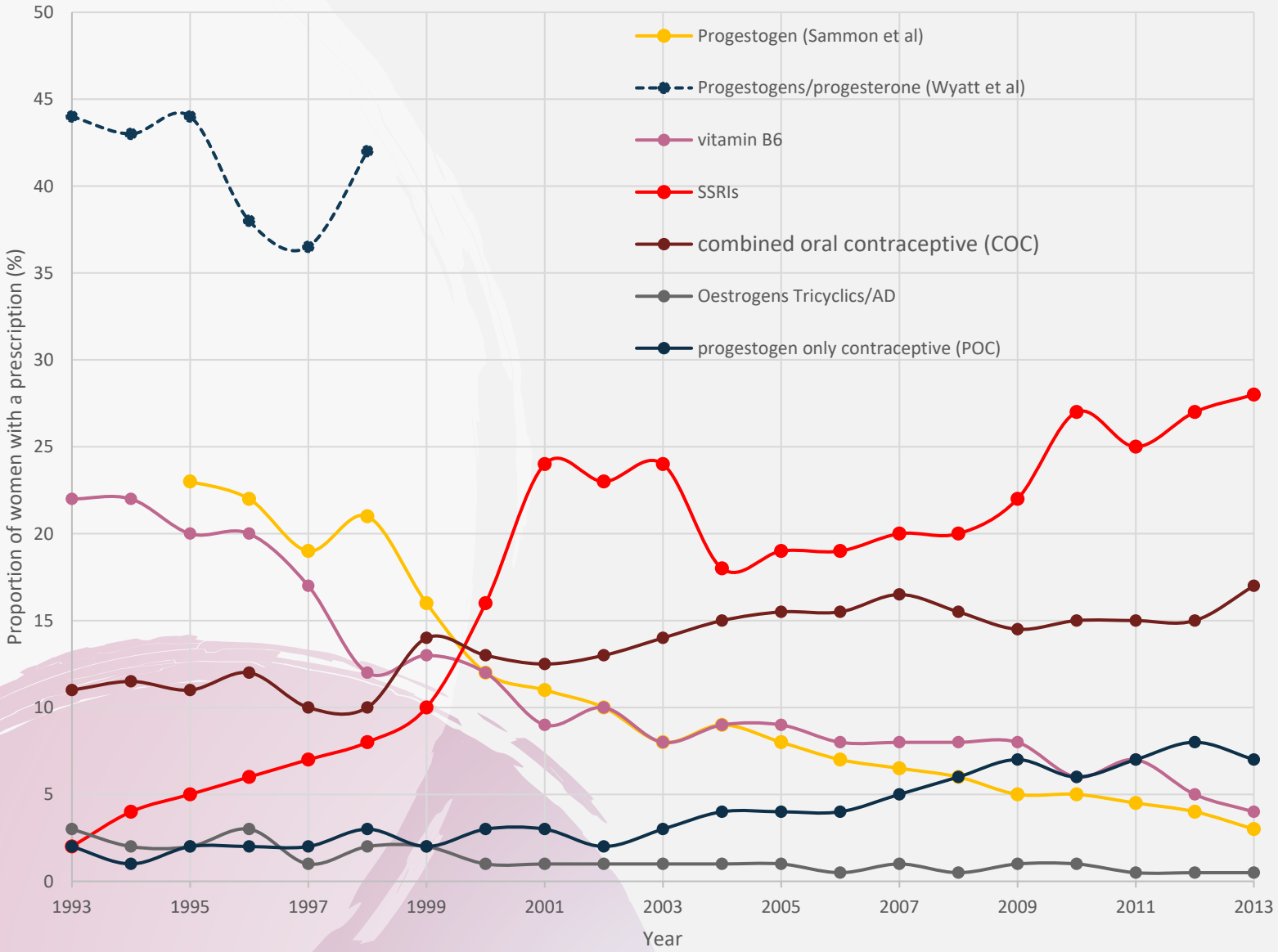
Private clinics, pharmacies, and counseling services (in the 80s)

A Weakly Supported Scientific Theory: Progesterone

Calendar Year Specific Proportion of women with Prescriptions

Progestogen prescription rates have dropped since the 1990s (the orange line) while SSRIs have risen significantly from around 2% in 1993 to 28% in 2013 (the red line).

Reproduced from Wyatt et al (2002) and Sammon et al (2016)



2. Quick sum-up:

A Weakly Supported Scientific Theory: Progesterone

Physician-centered pharmaceuticalization

- Progesterone as the recommended prescription without proper evidence for efficacy
- Gradually becoming a profitable industry

Industry-driven pharmaceuticalization

- Emerging in the 1980s.
- Influencing the regulatory agencies as we shall see
- PMS took a new form

3. It's all about the money: Sarafem

How PMS took the new form in the 1990s

APA

The American Psychiatric Association

Eli Lily

Prozac manufacturer

FDA

The Food and Drug Administration

3. It's all about the money: Sarafem

A brief timeline

1987

DSM-III, listed as LLPDD in appendix

(Late luteal dysphoric disorder, later known as premenstrual dysphoric disorder)

1991

Another committee revisited: "methodological problems still existed… that precluded a meaningful synthesis of the findings." (Gold, 1994)

1994

DSM-IV, listed as PMDD in both appendix and the depressive disorder Not Otherwise Specified

Why?

1999-2000

FDA approved Sarafem (rebranded Prozac) for PMDD

Why?

How?

2013

DSM-V, listed as PMDD in main body. PMDD was officially recognized despite some disagreement

3. Q1: Why was PMDD listed in both appendix and main body in DSM-IV

Two explanations

"a symptom pattern… has not been included in the DSM_IV Classification but… causes clinically significant distress or impairment…" (DSM-IV)

DSM-IV (1994), listed as PMDD in both appendix and the depressive disorder Not Otherwise Specified

"While appearing somewhat contradictory, this move was important commercially because it gave PMDD a precious item number—allowing doctors to prescribe drugs to treat the condition, and health insurers to fund them." (Moynihan and Cassels, 2005)

3. Q2: Why and how Eli Lilly was involved?

Patent expiration & losing market share

- Eli Lily: top seller of psychiatric drugs.
- Prozac was so profitable, approved in 1987, and achieved $21.1 billion in sales until 2001. (Langreth, 2001)
- Patent expired in 2001
- Sarafem is rebranded Prozac, packaged in pink and lavender

Reaching out to both researchers & FDA

- D.C. meeting with Lilly representatives, FDA staff, and sixteen key researchers (Monyhan, 2005)
- The minutes became an article claiming PMDD as a "distinct clinical entity" (Endicott et al, 1999)
- However, Sally Severino (one of the co-authors) said she never agreed that PMDD was a mental condition. (Fauber et al, 2017)

Clinical trials and application to the FDA

- Eli Lilly applied to the FDA to market fluoxetine (Prozac) for PMDD on Jan. 21, 2000. (Katz, 2000)
- "priced three and a half times higher than generic Prozac." (Angell, 2004)
- Funded a clinical trial, but it only "considered the 180 patients who completed the study, and not the 42% of subjects who dropped out." (Sufrin and Ross, 2008)

4. Discussion

Using one framework of the pharmaceuticalization by Abraham (2010)

Biomedicalism

New drugs reflect advances in biomedical science.

- Progesterone is no better than a placebo;
- The clinical trials on Sarafem (repackaged Prozac) was manipulated.

Medicalization

- Mutually reinforcing with pharmaceuticalization
- A two-way causality

Industry effort

After the 1980s:

- Sponsoring clinical trials
- Appealing to the FDA
- Marketing to the customers

Less obvious before the 1980s

consumerism

- Collaborative: seeking faster access to pharmaceuticals (yes)
- Adversarial: believe they are harmed (unclear)

Regulatory/policy

- The FDA was adamant regarding progesterone use
- But seems to be friendly to Eli Lilly
- Further research needed

4. Discussion: my arguments

From this case study:

The changing characteristics of pharmaceuticalization

- Before the 1980s:
  - Physcian-centered
  - Promoted by doctors, along with health writers, columnists, and journalists
- After the 1980s:
  - Industry-driven
  - Controls a bit of science
  - Close to regulatory agencies

The interplay between pharmaceuticalization & medicalization

- Before the 1980s:
  - Medicalization of premenstrual symptoms as PMS first
  - Pharmacetucalization, or progesterone as the treatment came after the medicalization of the symptoms as a diagnosis
- After the 1980s:
  - The complete medicalization of premenstrual depressive symptoms as PMDD serves as the justification for the pharmaceuticalization, i.e. the expansion of using Prozac.

References (1/3)

- Joan C. Chrisler and Paula Caplan, ‘The Strange Case of Dr. Jekyll and Ms. Hyde: How PMS Became a Cultural Phenomenon and a Psychiatric Disorder’, *Annual Review of Sex Research*, 2002, 13, 274-306, 276
- David M. Scott, ‘United States Health Care System: A Pharmacy Perspective’, *The Canadian Journal of Hospital Pharmacy*, 2016, 69(4), 306-315, 307.
- Peter Conrad, *The Medicalization of Society: On the Transformation of Human Conditions into Treatable Disorders* (Baltimore: The John Hopkins University Press, 2007), 5.
- John Abraham, ‘Pharamceuticalization of Society in Context: Theoretical, Empirical and Health Dimensions’, *Sociology*, 2010, 44, 603-622, 604
- Katharina Dalton, ‘Discussion on the Premenstrual Syndrome’, *Proceedings of the Royal Society of Medicine*, 1954, 48, 339-347, 344.
- Katharina Dalton, ‘Interview: Katharina Dalton, MD: Progesterone and Related Topics’, interview by Janet Beard, et al, *International Journal of Pharmaceutical Compounding*, interview date: April 21, published: September/October, 1999, 1-4
- Gareth Lloyd, ‘Book Review’, review of The Premenstrual Syndrome and Progesterone Therapy, by Katharina Dalton, *Journal of the Royal College of General Practitioners*, 1978, 28(193), 509.

References (2/3)

- Ellen C. G. Grant, ‘Katharina Dalton and progesterone dangers’, *BMJ*, November 1, 2004, 329, 1048.
- Alice J. Dan and Linda L. Lewis, *Menstrual Health in Women’s Lives* (Urbana and Chicago: University of Illinois Press, 1992), 65.
- Katrina M. Wyatt et al, ‘Prescribing patterns in premenstrual syndrome’, *BMC Women’s Health*, 2002, 2(1), 1-8, 4.
- Cormac J. Sammon et al, ‘Recording and treatment of premenstrual syndrome in UK general practice: a retrospective cohort study’, *BMJ Open*, 2016, ;6:e010244. doi: 10.1136/bmjopen-2015-010244, 3.
- Judith H Gold, ‘Historical Perspective of Premenstrual Syndrome’, in Judith H Gold and Sally K. Severino, eds., *Premenstrual Dysphorias: Myths and Realities* (Washington D.C.: American Psychiatric Press, Inc., 1994), 171-182, 177
- American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. (Washington, DC: American Psychiatric Association)
- Ray Moynihan and Alan Cassels, *Selling Sickness: how the world's biggest pharmaceutical companies are turning us all into patients* (New York: Nation Books)
- Robert Langreth, ‘Getting Off Prozac’, *Forbes*, April 30, 2001. https://www.forbes.com/forbes/2001/0430/072.html
- Jean Endicott, et al, ‘Is premenstrual dysphoric disorder a distinct clinical entity?’, *Journal of Women’s Health and Gender-Based Medicine*, 1999, 8(5), 663-679.
- John Fauber et al, ‘For one condition, the drugs came before the disorder’, *Milwaukee Journal Sentinel*, January 6, 2017.

References (3/3)

- Russell Katz (Director of Division of Neuropharmacological Drug Products, FDA) to Greg T. Brophy (Eli Lilly and Company, Inc.), July 6, 2000, Application number: NDA 18-936/S-058, approval letter. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/18936S58LTR.PDF
- Marcia Angell, *The Truth About the Drug Companies: how they deceive us and what to do about it* (New York: Random House, 2004
- Carolyn B. Sufrin and Joseph S. Ross, 'Pharmaceutical Industry Marketing: Understanding Its Impact on Women's Health', *Obstetrical & Gynecological Survey*, 2008, 63(9), 585-596. 588.