

Period Pill

Current costs and quality of life of women with premenstrual syndrome
and premenstrual dysphoric disorder

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About this report

This report has been prepared by THINC. for the Period Pill.

Colophon

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Executive summary

Aim and methods

In this report, the economic room for improvement in the management of premenstrual disorders including its associated costs and impact on quality of life was evaluated. The economic room for improvement is the maximum costs that can be saved if PMDD/PMS would be perfectly managed. Therefore, we performed a scoping review to identify the costs associated with PMDD/PMS to indicate which costs can be saved if PMDD/PMS would be perfectly managed (for instance by the Period Pill). The effectiveness of the Period Pill is not yet known and therefore not incorporated in the analysis. In addition, three expert consultations were performed to get additional insight on productivity losses and factors influencing these productivity losses.

Healthcare costs

The current economic burden associated with PMS/PMDD manifests itself primarily in productivity losses rather than health care utilization. The main cost-component of healthcare costs are medication costs; however, it is expected most women are untreated. Mean costs per menstrual cycle (cycle costs) are higher in the US than in Europe. In the US the mean SSRI cycle costs are around US\$16 for generic medication, while the mean oral contraceptive (birth control) cycle costs are around US\$67. If the Period Pill cycle costs would be above those costs, healthcare costs would increase in currently treated patients.

Productivity losses

Reported productivity losses in untreated women with PMS/PMDD are very heterogeneous. Women with severe PMS/PMDD experience workdays with 33% to 50% or less productivity for 3 to 7 days per cycle, while absenteeism varied from 0.83 to 3.6 days per menstrual cycle. Assuming the US salary of \$25.72 per hour, total losses per women were at least \$375 per cycle.

Productivity losses are expected to increase with severity of premenstrual symptoms. However, even in a study where women were included representative for the general population, mean productivity losses of \$154 per cycle per woman were shown, which emphasizes the burden of premenstrual symptoms in the general population. This indicates there is a large room for improvement in untreated or unsuccessfully treated women. However, the impact of successful treatment on productivity losses are not published yet.

Quality of life

Only one paper reported on utility values, the standard measure of quality of life in cost-effectiveness analyses.[±] In untreated women, when symptoms are most severe, the mean utility was 0.415, while immediately after menstruation, the mean utility was 0.964. Multiplying these values with the duration of symptoms resulted in a loss in quality of life of 0.18. In successfully treated women, after six cycles of SSRI treatment, quality of life recovered completely. This indicates there is a large room for improvement in quality of life in untreated women, but almost no room for improvement in quality of life for women successfully treated with SSRI's.

±A utility value of 0 represent death, while a utility value of 1 represent perfect health

Implications

This health economic analyses confirms the substantial room for improvement of the treatment of PMS/PMDD by THINC., an independent research group associated with the UMC Utrecht, academic medical center in the Netherlands. This room for improvement will differ for different patient groups depending on severity of the symptoms and whether women are already receiving treatment. A lot of women with PMS/PMDD are underdiagnosed and untreated. In part I of the THINC. analysis, it was reported that of women with PMS, only 20% receive psychological treatment, and of those estimated to have PMDD about 90% remains undiagnosed. It must be noted that these estimates are reported in scientific literature from almost 20 years ago.

In untreated women, successful treatment of PMS/PMDD can result substantial quality of life up to 0.18 per cycle and large productivity losses of at least \$375 per cycle can be prevented. Successful treatment in currently untreated women can thereby create an opportunity to increase quality of life and result in cost-savings.

In women who are already successfully treated, for instance with SSRI's, quality of life is reported to recover completely. Therefore, no room of improvement in quality of life exist in these women. As a result, to be able to be cost-effective, the Period Pill should aim for a comparable increase in quality of life, while at the same time result in cost-savings, for instance due to lower medication costs and/or a larger decrease in (currently unknown) productivity losses.

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1 Scope and deliverables of THINC. report

The Period Pill is currently investigating the introduction of a micro dosed novel psychoactive drug, for the treatment of symptoms associated with premenstrual disorders. In an earlier report THINC explored the clinical problem of premenstrual disorders and potential treatments, and countries with the highest potential to explore further for introduction of the Period Pill. In this report, the economic room for improvement in the management of premenstrual disorders including its associated costs and impact on quality of life will be evaluated. The economic room for improvement indicated which costs could be saved if PMDD/PMS would be perfectly managed, for instance by the Period Pill. The effectiveness of the Period Pill is not yet known and therefore not incorporated in this analysis. This will give the innovator and investors an indication of the probability for reaching cost-effective outcomes. This report provides a short summary of these findings.

2 Methods

For this early economic evaluation, we performed a scoping review to identify the costs associated with PMDD/PMS. PubMed searches were performed with the following search terms, after which potential other articles were sought with snowballing, meaning searching for relevant articles which are cited by or comparable with the found article:

“(premenstrual OR perimenstrual AND

- 1) (costs OR cost-effectiveness OR resource use)”*
- 2) (productivity loss OR work)”*
- 3) (quality of life)”*

In addition, three expert consultations were performed to collect their opinion on the heterogeneity of productivity losses as published in literature and their experience with productivity loss and working life in patients with PMS/PMDD. Experts were selected based on their overarching knowledge of PMS and PMDD and/or the interaction with working life. Experts were recruited by searching for (first or last) authors of key papers in PubMed, guidelines and the International Association for Premenstrual Disorders (IAPMD). The topic list used during the consultation is added as an Appendix.

3 Cost components of PMS and PMDD

3.1 Healthcare utilization

The economic burden associated with PMDD manifests itself primarily in reported productivity losses rather than health care utilization.(1) Most research on healthcare utilization was published around 20 years ago and the main cost-component of these healthcare costs were medication costs. Table 1 outlines medication as stated in the IAPMD guideline (3) and summarizes their approximated costs per menstrual cycle.(4,5) These medications are thus primarily indicated for PMDD patients. In part I of the THINC. analysis (other report), it was reported that of women with PMS, only 20% receive some kind of psychological treatment, and of those estimated to have PMDD

about 90% remains undiagnosed. It must be noted that these estimates are reported in scientific literature from almost 20 years ago.

Medication costs for SSRI's and oral contraception (birth control) are relatively low, medication costs are higher in the United States than in Europe and most interestingly, the difference between generic and brand medication is very pronounced in the US. These cost-prices of brand medication are given as an illustration, in a cost-effectiveness analysis, we would advise to take the generic medication as the comparator instead of brand.

In addition, women with PMS experienced an increased frequency of ambulatory health care provider visits and were more likely to accrue > \$500 in visit costs over 2 years. (2)

Medication costs per menstrual cycle	Dutch costs		US costs	
	Generic	Brand	Generic	Brand
SSRI's (in this example for 14 days)				
fluoxetine 20mg ("Prozac")	€ 0.56	€ 1.68	\$13.38	\$312.37
sertraline 50-150mg ("Zoloft")	€ 0.42	€ 3.92	\$18.79	\$240.70
paroxetine 20-30mg ("Paxil")	€ 0.56	€ 4.76	\$13.55	\$139.60
citalopram 20-30mg ("Celexa")	€ 0.42	€ 5.18	\$8.57	\$181.40
escitalopram 10-20mg ("Lexapro")	€ 0.56	€ 5.18	\$24.12	\$235.42
Oral contraceptive				
drospirenone 3mg/ethinylestradiol .02mg daily (e.g., "Yaz")	€ 2.24	€ 3.92	\$67.00	\$210.96

Table 1. First-line medications costs per menstrual cycle for generic and brand medication in the Netherlands (taken as representative for Europe) and the US.

3.2 Productivity losses

Productivity losses can be subdivided in absenteeism, which is missed (days of) work and presenteeism, which is decreased productivity while at work multiplied with the number of days at which they experience reduced productivity.

Reported productivity losses for PMS/PMDD in literature are very heterogeneous. All included studies are shown in the appendix and minimum and maximum values are given in Table 2.(1,2,7-10) One multinational study showed the heterogeneity is probably not because of a difference in setting, as productivity losses were consistent across countries.(6) All included studies are shown in the appendix and minimum and maximum values are given in Table 2.(1,2,7-10) Women with severe PMS/PMDD experience workdays with 33% to 50% or less productivity for 3 to 7 days per cycle. Especially the absenteeism results had a large heterogeneity with 0.83 to 3.6 days per menstrual cycle. However, it must be noted that the upper estimate of 3.6 days of absenteeism and 7 days with less productivity was far higher than estimates found in the other studies, and we therefore would consider this study to be an overestimation. Assuming the US salary of \$25.72 per hour (<https://ilostat.ilo.org/data/>) and 8 hours workdays results in at least $(0.83*8*25.72=)$ \$171 absenteeism and $(0.33*3*8*25.72=)$ \$204 presenteeism, with total losses of at least \$375 per menstrual cycle.

Productivity losses are expected to vary by severity of premenstrual symptoms women experienced and this is reflected in a paper of Chawla et al. (1) In this study, moderate PMS resulted in \$258

productivity loss per cycle, while \$296 per cycle was observed in severe PMS patients and \$744 in PMDD patients. Therefore, higher costs can be saved in women with higher severity of symptoms. However, even in the general population productivity losses are high, this is shown by Schoep et al. who evaluated productivity loss in all women, irrespective of presence of any PMS/PMDD symptoms. They found mean productivity losses of \$154 per cycle for the average women. (10)

The impact of treatment on productivity losses are not published yet. The impact of SSRIs on different aspects of working life in patients with PMS/PMDD is however reported in studies, for instance with the Sheehan Disability Scale (SDS). (11-13) These articles show an improvement in the SDS. Unfortunately, they cannot be translated into absenteeism and presenteeism.

	severe PMS/PMDD		All women
	Min	Max	Based on Schoep et al.
US salary per hour	\$25.72		\$25.72
Absenteeism, days	0.83	3.60	0.11
Absenteeism, costs	\$171	\$741	\$22
Presenteeism, days	3	7	1.94
Presenteeism, productivity loss (%)	33%	50%	33%
Total presenteesim loss	0.99	3.50	0.64
Presenteeism, costs	\$204	\$720	\$132
Productivity costs per cycle	\$374	\$1,461	\$154

Table 2. Minimum and maximum productivity losses reported in literature.

4 Productivity losses with PMDD and PMS: a qualitative addition

Three expert consultations were performed to collect their opinion on the heterogeneity of productivity losses as published in literature and their experience with productivity loss and working life in patients with PMS/PMDD. One gynecologist located in the US with various well-known publications on PMDD and two health psychologists (located in the Netherlands and the UK) who have published articles on the relationship between PMDD/PMS and work, and one of which was involved in the Dutch guideline on PMDD. In addition, all respondents have experience with PMS/PMDD patients in practice.

Measuring productivity losses

All respondents recognized the heterogeneity in results of productivity losses published in the scientific literature. Reasons for the heterogeneity that were mentioned were incomparable methods used, heterogeneity in severity of symptoms in included patients and/or heterogeneity in definition of PMS/PMDD.

All respondents recommended to measure productivity losses in a prospective way, a day-to-day journal was given as an example, because the pattern of the disease. However, a journal would be a lot of work for women, especially for women with symptoms. Experts mentioning day-to-day

reported is particularly important because, usually, in cost-effectiveness analyses, patients are asked to estimate their productivity losses in the previous 4 to 6 weeks.

Patient's impact on working life

Two respondents had a clear view on the impact on their patient's working life. They confirmed that impact might be related to the severity of symptoms, with less productivity for a few days in patients with mild symptoms, to termination of a contract because of a conflict in patients with severe PMDD. One respondent added that severity of problems did not always correspond to work problems. She added that work factors such as having control over their job and being able to adapt their work, working in a trusting organization and a supportive culture allow women to work flexible and give them the opportunity to compensate in a safe way, which can prevent work problems. The respondent from the United States indicated to focus completely on social interaction with family and friends and did not ask patients on the impact on their working life.

Two respondents indicated that in patients with mild symptoms, women experience less productivity and might compensate for this later. However, they noted it is their self-perception, and actual output is then not known subjectively. It is natural to have flows in work, but women might feel guilty about it. Two respondent said women with PMS and PMDD might be prone to compensate for this in periods without symptoms. One respondent referred to this phenomenon as a 'sawtooth pattern'. Both experts described a downward spiral in which stress of compensating work might exacerbate symptoms in the next cycle.

Impact of medication on working life

Respondents indicated that, in their experience, medication and psychotherapy helped patients in their symptoms and in their social interaction. However, not all patients benefit from it and all respondents clearly stated management could be improved. Two of the respondents also emphasized that improvements in lifestyle factors and working related factors should first be considered before starting medication.

One of them explicitly stated incidental medication could potentially break the downward spiral in women and prevent more severe symptoms and productivity losses in women, partly also by giving women a feeling of control over their symptoms.

"If the medication would work fast, then that would be nice. It could break the sawtooth pattern. Then you might also be able to stop medication after a few cycles."

"I think so, that SSRI will help for the working life. It does give you a layer giving you no high and no lows. For a routine job, that might not matter, but it does for knowledge work or in the creative sector, we saw some people quit SSRI's even though it did seem to work for them. They said they lost their creativity."

Other comments on market opportunity

Even though it was not the aim of the interviews, we would like to share that all respondents indicated that other treatment options for PMDD (and PMS) patients would be useful.

“If it looks like it could help, it is worth a trial. I need to know more information about it really. But it sound interesting, psychoactive drugs they have been used for a variety of psychological and medical disorders.”

One respondent indicated that treatment is now often based on hypes instead of evidence-based guidelines. In addition, one respondent added that in general not enough is known about the disease itself and for instance lifestyle factors influencing it. This respondent expressed Combined with the description of the medication, this respondent expressed:

“It would be a very interesting trial.”

BACKGROUND INFORMATION ON ECONOMIC ANALYSES

Normally, the main outcome of a formal (late-stage) economic evaluation is the cost-difference and the effect-difference of the intervention compared to current treatment. With cost-savings and increased effectiveness, the intervention is cost-effective. If the intervention has an increase in costs compared to no treatment or alternative treatment, it could still be cost-effective if quality of life would be improved. Then, the main outcome of the study will be the Incremental Cost Effectiveness Ratio (ICER), which is calculated as the difference between the costs of the innovation and standard care divided by the difference between effects of the innovation and standard care (as reflected in Formula 1).

$$ICER = \frac{\Delta Costs}{\Delta Effects} = \frac{Costs Innovation - Costs Standard Care}{Effects Innovation - Effects Standard Care} \quad (\text{Formula 1})$$

The effects are usually expressed in quality-adjusted life years (QALYs), which is a generic measure of disease burden, combining the quality and the quantity (years) of life lived. Quality of life is measured by using a number between 0 to 1, to which 0 equals death and 1 equals perfect health and these values are usually called “utilities”. 1 QALY can therefore correspond to 1 year in perfect health or for instance, 2 years with 0.5 quality of life. As such, the ICER can be interpreted as the

5 Quality adjusted life years

Even if the Period Pill would not be cost saving compared to no treatment or alternative treatment, it could be cost-effective if quality of life would be improved. Some papers reported the impact of PMDD/PMS on quality of life in patients using and not using SSRI's, papers on the impact of oral contraception were not found. However, most of these studies did not report utilities, ranging from 0 to 1 as used in economic analysis.

For instance, Yang et al concluded PMDD is associated with substantial burden on both physical and mental aspects of health-related quality of life (HRQoL) using the SF-12.(14) Other articles were in accordance with these findings and used various tools to measure quality of life. One study concluded that if treatment with SSRI's is effective, it can quickly restore HRQoL to levels observed in the general population. Two studies evaluating oral contraceptives reported improved general functioning, QoL measures, as well as clinician rating of the symptoms and QoL compared with placebo(15,16).

Only one paper reported utility values, which are collected with the EQ5D, an often-used measure in cost-effectiveness analyses. In this cost-effectiveness paper, Kamagata et al. found that when symptoms were most severe (immediately before menstruation in most cases) the mean EQ-5D score was 0.415, while immediately after menstruation (follicular phase) when PMDD symptoms were absent, the mean EQ-5D was 0.964.(17) Using these values and the number of days with symptoms, a mean EQ-5D score per menstrual cycle of 0.789 was calculated; corresponding to a loss in quality of life of 0.18. After six cycles of SSRI treatment, the mean EQ-5D score per menstrual cycle recovered completely to 0.979 in successfully treated patients.

The results from Kamagata et al. indicate there is almost no room for improvement in quality life for patients successfully treated with SSRI's. However, in contrast, the room for improvement in quality life is large in patients discontinuing SSRI's or not receiving any treatment.

6 Implications for cost-effectiveness

The opportunity for the Period Pill to be cost-effective depends on the above-described outcomes of current care, the intended group of women (severity of symptoms and current groups), the effectiveness of the Period Pill and the cycle costs of the Period Pill. Because the potential effectiveness and the cycle costs of the Period Pill are currently unknown, some potential (what if) scenarios were drafted below to illustrate potential consequences.

In untreated or unsuccessfully women, an opportunity for an increase in quality of life exist. Without an increase in quality of life, cost-savings could be achieved if the Period Pill cycle costs and productivity losses combined are lower than the current productivity losses. For instance, if the Period pill would cost \$25 for one cycle, and it could prevent a mean of one hour of absenteeism, or can improve a one day 12.5% productivity, use of the Period Pill would already lead to cost-savings. In addition, with no cost-savings, but an increase of 0.1 in quality of life, Period Pill costs of \$5000 per cycle would still lead to a cost-effective treatment compared to no treatment, because the ICER is below most of the willingness-to-pay thresholds.

In successfully treated women, the quality of life loss of women treated with the Period Pill should be restored to none for the Period Pill to be able to be cost-effective. If quality of life loss of the

Period Pill is restored to none, then the Period Pill cycle costs and productivity losses combined should be lower than the treatment costs and productivity losses combined of current treatment. Thus, with each increase of \$25 of cycle costs for the Period Pill, an additional one hour of work absence, or an improvement of 12,5% in productivity for one day is necessary to result in cost-savings.

7 Discussion

The health economic analysis confirms the room for improvement of the treatment of PMS/PMDD by THINC., an independent research group associated with the UMC Utrecht, academic medical center in the Netherlands. The economic burden and burden in social life and quality of life has widely been published on. However, most of the literature we could use was published around 20 years ago. Some of the more recent papers we included were on productivity losses (in untreated women). Even though this limited the certainty of results of the potential impact of new medication, the burden in quality of life and productivity losses in PMS/PMDD patients is clear and it does only further emphasize the market opportunity for new medication.

Substantial room for improvement in untreated or unsuccessfully treated patients

The room for improvement will differ for different patient groups depending on severity of the symptoms and whether women are already receiving treatment. As indicated previously in the report, a lot of women with PMS/PMDD are underdiagnosed and untreated. In these women, substantial quality of life can be gained of up to 0.18 per cycle and large productivity losses of at least \$375 per cycle can be prevented, thereby creating an opportunity to induce cost-savings.

In successfully treated patients there is room for improvement, but only in costs

However, in women who are already successfully treated, for instance with SSRI's, quality of life is reported to recover completely. Therefore, no room for improvement in quality of life exist in these women. Studies on the effect of SSRI's on productivity losses are currently lacking. Future studies should be performed to compare the effectiveness of the Period Pill compared to SSRI's in effectiveness, productivity losses and other healthcare use.

Productivity loss is substantial also compared to other well-known diseases (such as migraine).

Even though large heterogeneity in reported productivity loss was observed between published trials, productivity losses were in the same range as other well-known diseases in premenopausal women with at least 0.83 day per menstrual cycle (approximately one month) missed days and at least 0.99 presenteeism. For instance, a scoping review published missed working days in migraine patients from 3 hours to 0.95 days per month and presenteeism of 1.1 to 3.2 days in episodic migraine.(18) Therefore, we would conclude productivity loss, and therefore also the room for improvement, is large. However, endometriosis has even larger productivity losses, in one US study, endometriosis patients reported an average weekly loss of 6.34 work hours due to endometriosis.(19) In a multi-country study, each affected woman lost on average 10.8 hours of work weekly.(20)

Productivity loss is important for several stakeholders.

Productivity losses are indirect costs and therefore part of the societal perspective but not included in the healthcare perspective. However, we would argue productivity losses are important for several stakeholders. For instance, many women receive insurance via self-insured companies in the US, these companies would obviously also benefit from a reduction in productivity losses. Another example is that in the Dutch setting the societal perspective is preferred to be included in the health insurance basic package.

8 Recommendations for future research

- The availability of data permitted this analysis, however with the uncertainties as described. Additional early health economic modeling is not expected to have additional value until after clinical trials are performed.
- If clinical trials will be performed, it is essential to perform the economic analysis alongside the clinical trial, collecting costs, productivity loss and quality of life in included patients.
- The collection of costs, productivity loss and quality of life data is recommended to perform at short intervals. Expert indicated the pattern of the disease might influence patients' recall. Typically, recall of 4 to 6 weeks is used in cost-effectiveness, but experts advised to collect data on day-to-day basis in these patients.

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9 Appendix: productivity losses published in all included sources

Indirect costs	Heinemann	Borenstein 2007	Borenstein 2003	Schoep 2019
Type of patients	<i>Severe PMS and PMDD</i>	<i>PMS patients</i>	<i>PMS patients</i>	<i>All women</i>
Absenteeism, days missed per cycle	8% more than 8 hours	3.6	1.2	0.11
Presenteeism, productivity loss %			50%	33%
Presenteeism, days per month patients	4.5	7	3	1.94
Presenteeism productivity * days				

Indirect costs	Chawla			Dean
Type of patients	<i>PMDD</i>	<i>Moderate</i>	<i>Severe</i>	<i>PMS</i>
Absenteeism, days missed per cycle	0.98	0.39	0.83	1.2
Presenteeism, productivity loss %	22%	7%	12%	50%
Presenteeism, days per month patients				3
Presenteeism productivity * days	2.64	0.87	1.44	

11 Appendix: questions ask in the expert consultations

- What are your first thoughts if you think about the relationship of PMDD and PMD and their influence on work?
- What do you think are your most important findings of your already performed (and potentially currently undergoing) research?
- What are your thoughts on the heterogeneity in work absence and productivity as published in current literature?
- Which factors do you think are most important in influencing productivity loss due to PMDD and PMS?
- Which women have the highest productivity loss due to PMDD and PMS?