THE EFFECT OF AN OVER-THE-COUNTER PRODUCT IN THE TREATMENT OF PREMENSTRUAL TENSION SYNDROMES

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CHAPTER I

INTRODUCTION

Man has long recognized a wide variety of changes that frequently occur in tandem with the menstrual cycle. Hippocrates, the father of medicine, attributed delusions, mania, thoughts of suicide and other symptoms to "retained menstrual blood" in his treatise on "The Sickness of Virgins" (Wichita Eagle-Beacon, 1986).

Although these cyclical changes in women have long been recognized, the explanation for the wide range of behavioral, emotional and physical symptoms that occur on a regular basis, month after month, between ovulation and menstruation, has remained an enigma. There is no universally accepted clinical definition for the premenstrual symptoms and no lab test to aid diagnosis. As a result no one has been able to develop a unifying explanation for the possible causes of these symptoms or determine the best way to treat the problem. Researchers cannot even come to a consensus on what to call this symptom complex that occurs during the luteal phase of the menstrual cycle.

Robert Frank, an American gynecologist, first coined the term premenstrual tension (PMT) for a group of symptoms occurring during the premenstruum (Frank, 1931). Greene and

Dalton (1953), proposed the term which is probably the most widely used today, the premenstrual syndrome (PMS), so called because of the cyclicity of the symptoms and their relationship to the premenstrual phase. Then Parker (1960) took Frank's original label and combined it with Greene and Dalton's modification and called this symptom complex the premenstrual tension syndrome.

These terms imply one syndrome, but Moos (1968) found many clusters of premenstrual symptoms which suggested many syndromes. Because nervous tension is one of the most common complaints, Abraham (1983), in recognition of Frank's initial contribution, and to acknowledge the large number of syndromes Moos had identified, developed the term premenstrual tension syndromes (PMTS). This is the term that will be used throughout this paper.

Premenstrual Tension Syndromes

Definition of PMTS

In addition to the lack of unanimity regarding what to call this symptom complex, researchers have also been unable to come to a consensus on a clinical definition of PMTS. However, even though there is no universally accepted definition of PMTS, a clear definition is necessary for the development of valid criteria for diagnosing the problem, grading its severity, and assessing responses to treatment (Abraham, 1983). Therefore, in order to grapple with this confusing disorder, and to maintain consistency and compara-

bility with other studies, Abraham's definition of PMTS, which is as follows, will be used in this paper.

> PMTS is a symptom complex occurring during the luteal phase of the menstrual cycle, becoming progressively worse, interfering with familial, social and work-related activities and improving after the onset of menses. This definition implies that the symptoms are absent or mild during the week after the end of menses and moderate or severe during the week before menses (Abraham, 1983, p. 447).

Incidence of PMTS

PMTS research is hampered not only by the lack of a clear definition of PMTS, but also by the lack of specific inclusion-exclusion criteria, and the lack of a diagnostic test to determine the presence of PMTS. As a result, it is nearly impossible to determine how many women suffer with PMTS. If statistics are based on mild mood changes associated with the menstrual cycle, then nearly every menstruating woman has PMTS. Indeed, O'Brien (1982) indicated the incidence of PMTS had been reported to be as high as 95 percent. However, if criteria are based on more severe symptoms or on the number of women seeking help, the numbers are much lower. Norris and Sullivan (1983) indicated only 10-15 percent of menstruating women experience symptoms that disrupt their lives.

The incidence of PMTS is said to increase with age, parity, a history of pre-eclampsia, exposure to stress, when living with a male, and as a result of a lack of exercise (Abraham, 1980). Smith (1976) suggested PMTS occurs less

often in schizophrenics and women taking oral contraceptives. However, once again, estimates of the incidence of PMTS will vary depending on inclusion-exclusion criteria and the source of the sample studied.

Symptoms of PMTS

Symptoms associated with the menstrual cycle have been alluded to for eons. The symptoms of PMTS will generally occur 7 to 14 days prior to the onset of menses. The onset of symptoms will vary among women, but it will usually occur at the same time in the cycle of any one woman.

There is a long list of symptoms of PMTS that encompasses almost every medical specialty. The most common psychological symptom of PMTS is tension, which is why this disorder is called premenstrual tension syndromes. One of the most common physical symptoms experienced is edema, which manifests itself in swollen ankles, a puffy face, or enlarged, tender breasts. Following are some of the most common symptoms of PMTS:

1. Tension, anxiety
2. Irritability, anger, aggression, hostility
3. Mood swings, crying spells, sadness
4. Swelling of extremities, bloating, weight gain
5. Fatigue, lethargy, insomnia
6. Headache, breast tenderness, joint/muscle pain
7. Decreased concentration, indecision, paranoia
8. Nausea, diarrhea, constipation

9. Anorexia, compulsive eating, increased thirst
10. Acne, recurrence of herpes infection
11. Clumsiness, dizziness, seizures
12. Changes in libido, heat flashes
13. Decreased motivation, social isolation, poor impulse control.

Clare (1983) and Koeske (1983) have suggested that symptoms of PMTS may be the result of interactions among biological, psychological, social, cultural, and environmental stress factors. Others have found evidence that indicate a woman's negative expectations and attitudes about menstruation have an affect on how they view their PMTS symptoms (Ruble, 1977; Brooks, Ruble and Clark, 1977; Koeske and Koeske, 1975).

Possible Causes of PMTS

What causes some women, but not others, to have premenstrual problems? A plethora of theories regarding the possible causes of PMTS have been postulated since Frank (1931) first identified the symptom complex. However, because researchers are operating without a standard definition of PMTS and without a diagnostic test to determine the presence of PMTS, no theory can be regarded as more than an hypothesis (Ruble and Brooks-Gunn, 1979).

Nevertheless, researchers have provided a variety of theories regarding the etiology of PMTS. The most popular theories point to the gonadal hormones, progesterone and

estrogen, as the cause of PMTS. Rubinow and Roy-Byrne (1984) found a great deal of conflicting data regarding altered gonadal steroid activity and suggested much of the diversity could be attributed to methodological flaws, such as failure to carefully define the syndrome, formulate a set of answerable questions, and select an homogeneous population.

Endocrine anomalies are almost universally implicated as the cause of PMTS, and aldosterone and prolactin have also been theorized as possible causes of PMTS. However, the aforementioned problems with study design continue to produce conflicting results and necessitate further investigation before the relationship between these hormones and PMTS can be determined.

Numerous nonhormonal theories have also been offered as possible causes of PMTS, including, nutritional deficiencies, prostaglandins, hypoglycemia, essential fatty acid metabolism abnormalities, disturbances in neuroendocrine function, allergies, altered brain activity, and numerous psychological hypotheses. None of these theories has been substantiated, and it is unlikely any single cause is responsible for the myriad of symptoms associated with PMTS, as Reid and Yen (1981) concluded when they described PMTS as a multifactorial neuroendocrine disorder. Until the methodological flaws pointed out by Rubinow and Roy-Byrne (1984) are corrected, the exact causes of PMTS will remain

uncertain and results of PMTS studies involving possible causes will continue to be contradictory.

Treatments for PMTS

Treatments for PMTS are as varied as theories about its etiology and range from self-help measures to hysterectomy. Henriksen (1961) did a survey of PMTS literature and found 327 items being promoted as specific or adjuvant therapy for PMTS. A survey of physicians who had requested information from the PMS Action Committee revealed that the most commonly recommended treatments for PMTS were diet, exercise, vitamins, and progesterone. The least available and least recommended treatments were antiprostaglandins, bromocriptine, and support groups for patients and their families (Lyon and Lyon, 1984). The efficacy of the numerous pharmacologic and nonpharmacologic treatments for PMTS is based largely on anecdotal evidence as a result of the consistent failure to investigate the proposed treatments with placebo-controlled, double-blind studies. This is especially critical in studies involving PMTS due to the high placebo response rate of 30%-80% in patients with PMTS (Smith and Youngkin, 1986).

The focus of this paper will be on the effectiveness of a pharmacologic treatment in the reduction of PMTS symptoms. According to True et al. (1985), of the many pharmacologic treatments that have been proposed, none has been shown to be reliably effective. This is the result of the studies of

PMTS treatment modalities being compromised by the same methodological flaws that hamper research into the cause of PMTS. The unknown etiology, the unclear definition, and the lack of objective parameters to measure complicates the discovery of an effective PMTS treatment. Also, most studies have been conducted with small, heterogeneous samples and have consistently failed to design studies incorporating placebo-control groups.

Statement of the Problem

This study investigated the effect of an over-the-counter (OTC) preparation consisting of 500 mg. of acetaminophen, 25 mg. of pamabrom, and 15 mg. of pyrilamine maleate in the relief of PMTS symptoms in women who met the established criteria for PMTS.

Hypotheses

1. There will be no significant difference in the scores for all PMTS symptoms when the pre-test menstrual symptom questionnaire (MSQ) score is compared to the subsequent MSQ scores obtained after the active treatment and placebo has been administered.
2. There will be no significant difference in the scores for specific PMTS symptoms found in the four PMTS subgroups Abraham (1983) has defined when the pre-test MSQ scores for the four PMTS subgroups are compared to the

subsequent MSQ scores obtained after the active treatment and placebo has been applied.

3. There will be no significant difference in the scores for all PMTS symptoms when comparing the active treatment to the placebo.
4. There will be no significant difference in the scores for the specific PMTS symptoms found in the four PMTS subgroups when comparing the active treatment to the placebo.
5. There will be no significant difference in the scores for PMTS symptoms between the group on the birth control pill and the group not on the birth control pill.

Limitations of the Study

1. The MSQ was not constructed using standardized psychometric procedures that would ensure internal consistency, reliability, reduction of redundancy, and cohesiveness of subgroups (Rubinow and Roy-Byrne, 1984).
2. The MSQ is not a diagnostic test which measures objective parameters, but rather relies on subjective reporting of symptoms.
3. There is no universally accepted definition of PMTS.
4. The symptoms of PMTS are widely variable and may not appear every cycle.

6. The type of birth control pill used by subjects was not identified.

Delimitations of the Study

1. The study was limited to an investigation of an OTC drug containing 500 mg. of acetaminophen, 25 mg. of pamabrom, and 15 mg. of pyrilamine maleate.
2. The symptoms of PMTS were measured using a MSQ developed by Abraham (1983).
3. Only subjects who indicated moderate or severe PMTS during the week before menses or mild or absent PMTS during the week after menses, according to their score on the pre-test MSQ, were included in the study.
4. The subjects were limited to 58 women who were menstruating regularly, did not suffer from regular headaches, and were not currently being treated for menstrual distress.
5. The study was conducted over two consecutive menstrual cycles with the active treatment and placebo administered in a double-blind fashion and PMTS symptoms recorded on the MSQ after each treated cycle.

Assumptions

1. It is assumed that the protocol for the ingestion of the treatments and subsequent evaluation of symptoms was maintained.

2. It is assumed that even though PMTS has no accepted clinical definition, nor an objective diagnostic test, the MSQ is an effective and acceptable measurement instrument for the presence and severity of PMTS symptoms.

Definition of Terms

Conceptual

Syndrome. A set or constellation of symptoms or signs that together characterize or identify a specific disease or disorder.

Premenstrual Tension Syndrome (PMTS). A symptom complex occurring during the luteal phase of the menstrual cycle, becoming progressively worse, interfering with familial, social and work-related activities and improving after the onset of menses (Abraham, 1983).

Placebo. A medically inert substance formulated to mimic, in color and form, an active substance.

Over-the-Counter (OTC) Drug. A drug that the Federal Drug Administration (FDA) accepts as safe for self-medication. An OTC drug can be used by consumers for disorders they diagnose themselves and treat by following the directions on the label without advice from a physician.

Analgesic. A drug like aspirin or acetaminophen that decreases pain.

Antihistamine. A drug like pyrilamine maleate used to treat an allergy by counteracting the effects of histamine, which is manufactured by certain cells in the body.

Diuretic. A drug like pamabrom that tends to decrease the amount of fluid retention.

Functional

Premenstrual Tension-Anxiety (PMT-A). This subgroup is representative of those women who experience anxiety, irritability and nervous tension (Abraham, 1983).

Premenstrual Tension-Hydration (PMT-H). This subgroup is associated with symptoms of water and salt retention, abdominal bloating, mastalgia and weight gain (Abraham, 1983).

Premenstrual Tension-Carbohydrates (PMT-C). This subgroup is characterized by craving for sweets, increased appetite and indulgence in eating refined sugar followed by palpitation, fatigue, fainting spells, headache and sometimes the shakes (Abraham, 1983).

Premenstrual Tension-Depression (PMT-D). This subgroup is potentially the most dangerous because symptoms include depression, withdrawal, confusion, insomnia and forgetfulness (Abraham, 1983).

Mild PMTS. The score on the Menstrual Symptom Questionnaire (MSQ) is less than five for PMT-A and PMT-H, less than six for PMT-D and less than seven for PMT-C (Abraham, 1983).

Moderate PMTS. The score on the MSQ is between five and eight for PMT-A and PMT-H; between six and ten for PMT-D; and between seven and twelve for PMT-C (Abraham, 1983).

Severe PMTS. The score on the MSQ is between nine and twelve for PMT-A and PMT-H; between eleven and fifteen for PMT-D; and between thirteen and eighteen for PMT-C (Abraham, 1983).

Description of Instrument

The Menstrual-Symptom Questionnaire (MSQ) utilized in this study is a retrospective questionnaire developed by Abraham (1980). The MSQ consists of nineteen symptoms arranged into four subgroups. The MSQ is used as a screening tool to detect the presence and severity of PMTS and then used after the treatment is applied to evaluate any symptom changes that may have occurred as a result of the treatment (see Appendix).

CHAPTER II

A SELECTED REVIEW OF LITERATURE

The Food and Drug Administration (FDA) Advisory Review Panel on Over-the-Counter (OTC) Miscellaneous Internal Drug Products (hereinafter referred to as Miscellaneous Internal Panel) reviewed 73 active ingredients for relieving symptoms of PMTS and menstrual distress. Ten of the ingredients were classified as Category I, 58 ingredients as Category II, and six ingredients as Category III (Fed. Reg., 1982). Category I means conditions under which OTC menstrual drug products are generally recognized as safe and effective and are not misbranded. Category II means conditions under which OTC menstrual drug products are not generally recognized as safe and effective or are misbranded. Category III means conditions for which the available data are insufficient to permit final classification at this time (Fed. Reg., 1982).

The product under investigation in this study, a combination of an analgesic, acetaminophen; a diuretic, pamabrom, and an antihistamine, pyrilamine maleate, was classified as Category I because the individual ingredients were classified as Category I. The present classification of these ingredients as a treatment for PMTS has only appeared in an Advanced Notice of Proposed Rulemaking (Fed. Reg., 1982),

which is the first stage in the FDA's three stage approval process for OTC drugs. This means that the FDA has not yet fully evaluated the report by the Miscellaneous Internal Panel. At this stage of the approval process, the panel's findings were issued to generate public comment before the FDA made any decision on the Miscellaneous Internal Panel's recommendation (Fed. Reg., 1982). So, even though the product has gained initial approval, the FDA will continue to evaluate results of studies involving these products before making a final determination.

Pamabrom

The use of diuretics for PMTS was based on the observed retention of water and electrolytes in so many women who experienced premenstrual distress. According to Velacott and O'Brien (1987), PMTS has long been considered a disorder in which fluid retention plays a major role. However, the role of diuretics as a PMTS treatment is still unsettled as investigations into the efficacy of diuretics in the treatment of PMTS have produced widely variable results. Nevertheless, numerous etiologic theories and treatment protocols are based on this premise.

The diuretic under investigation in this study, pamabrom, a xanthine derivative, was approved for OTC marketing in 1952 as a single entity diuretic and in combination with pyrilamine maleate, an antihistamine. More recently, the Miscellaneous Internal Panel reviewed two studies by

Hutcheon (1977, 1981) and a study called the Wisconsin Study (1978). The Miscellaneous Internal Panel considered one Hutcheon Study (1981) and the Wisconsin Study (1978) to be only suggestive of the effectiveness of pamabrom as a diuretic, but based upon the results of the earlier Hutcheon study (1977) the panel concluded that pamabrom was generally recognized as a safe and effective diuretic in removing the symptoms associated with water accumulation during the premenstrual period (Fed. Reg., 1982).

Despite the widely variable results obtained from studies involving diuretic therapy for PMTS and despite the fact that the underlying fluid retention theory remains in doubt, diuretics appear to have a role in the management of PMTS. According to the Miscellaneous Internal Panel, the only proper use of OTC diuretics is in eliminating water accumulation during the premenstrual and menstrual periods, which relieves the symptoms of water weight gain, bloating, swelling, and/or a full feeling (Fed. Reg., 1982). The safe use of OTC diuretics for PMTS is based on the fact these conditions are self-diagnosable, limited in duration, occur intermittently, and are not symptoms of a potentially serious underlying disorder (Fed. Reg., 1982).

Pyrilamine Maleate

The rationale for using pyrilamine maleate as a treatment for PMTS is based on a theory that was reported in the Wisconsin Study (1978) that suggested the PMTS sufferer is

allergic to her own steroids. A study based on this aforementioned theory also reported in the Wisconsin Study (1978) demonstrated that the amount of histamine in the body increases and decreases with fluctuations in estrogen levels during the menstrual cycle. These theories provide the basis for the hypothesis that the administration of an antihistamine, like pyrilamine maleate, could prevent or relieve vascular congestion caused by abnormal water retention. Other studies involving pyrilamine maleate demonstrated local anesthetic activity (Dews and Graham, 1946; Haranath, 1954) and found that pyrilamine maleate exerted a mild analgesic action (Hewer and Keele, 1948).

More recent studies performed to document the effect of pyrilamine maleate on symptoms of PMTS were submitted by Chattem Inc. to the FDA & Advisory Review Panel on OTC Miscellaneous Internal Drug Products. In the Wisconsin Study (1978) 194 women participated in a placebo-controlled, double-blind, single cross-over design study to assess the effects of pyrilamine maleate and pamabrom on the symptoms of PMTS when administered separately and in a fixed combination. The results of the study indicated that pyrilamine maleate significantly reduced the symptoms of tension, irritability and cramps. The Boston Study (1981) confirmed the findings of the Wisconsin Study (1978) and expanded the effect of pyrilamine maleate on the reduction of the intensity of symptoms associated with PMTS by including backache

and swelling in the list of symptoms improved by pyrilamine maleate.

Even though the Miscellaneous Internal Panel recommended that pyrilamine maleate be classified as Category I "for the relief of emotional changes related to the premenstrual period" and "for relief of water retention symptoms," the FDA was concerned that the data that were reviewed were too conflicting and may not be sufficient to provide general recognition of effectiveness (Fed. Reg., 1982). As a consequence, the FDA suggested that products containing pyrilamine maleate as a single ingredient and being promoted as a treatment for PMTS should not be marketed at this time.

Acetaminophen

The Miscellaneous Internal Panel has also reviewed submissions proposing the use of acetaminophen for the treatment of PMTS. The Miscellaneous Internal Panel concluded that acetaminophen was generally recognized as safe and effective for OTC use in relieving pain of the premenstrual syndrome (Fed. Reg., 1982).

The Miscellaneous Internal Panel came to this conclusion based on information provided by the Advisory Review Panel on OTC Internal Analgesic and Antirheumatic Drug Products (hereinafter referred to as the Internal Analgesic Panel). The Internal Analgesic Panel concluded that OTC analgesic drugs are intended to alleviate the symptoms of mild to moderate pain, specifically the type of pain that is

self-limiting and requires no special treatment or prior diagnosis by a physician (Fed. Reg., 1977). The Miscellaneous Internal Panel considered pain associated with PMTS to be in that category and concluded that any analgesic that had been given a Category I designation by the Internal Analgesic Panel for a label claim of "For the temporary relief of occasional minor aches, pain, and headaches" (Fed. Reg., 1977, pp. 35351) may be used with a label claim relating to the relief of pain associated with PMTS (Fed. Reg., 1982).

Combination Products

Studies have been done involving acetaminophen, pamabrom, and pyrilamine maleate individually, but no studies have been done involving a preparation consisting of these three ingredients in combination. The FDA allowed products containing 500 mg. acetaminophen, 25 mg. pamabrom, and 15 g. pyrilamine maleate to be marketed based on the conclusion of the Miscellaneous Internal Panel that the addition of any Category I analgesic to a diuretic/antihistamine combination would result in a Category I classification because all of the individual ingredients had a Category I designation.

Despite the fact that this combination of acetaminophen, pamabrom, and pyrilamine maleate has been classified as Category I for the treatment of PMTS, there is still a great deal of uncertainty regarding their use and effectiveness. One complicating factor in the therapeutic

management of PMTS is that PMTS responds to almost anything, including placebos, at least for a while (Hopson and Rosenfeld, 1984). As a result, claims are often made that certain drugs for PMTS alleviate all symptoms and cure all patients. To date, most prescription drugs and OTC medications have not proven to be any more effective than placebo in combating symptoms of PMTS (Switzer, 1983). It appears no one drug or behavioral therapy offers relief to all because PMTS manifests itself through so many symptoms that it makes a universal treatment approach unrealistic.

Based on the conflicting reports concerning PMTS treatments, clinicians have taken two approaches to therapy according to O'Brien (1982). The first approach is one drug cures all. For instance, progesterone has often been promoted as a "cure" for PMTS. The second approach involves the administration of various drugs in a random fashion based on the therapist's clinical experience with the drugs, otherwise known as a shot gun approach. For example Chakmakjian (1983) suggested the following treatment regimen for PMTS. First, the patient and her family should be counseled and given support. Recognition of the condition as physiologic could aid the patient in coping with the symptoms. Second, for patients with moderate to severe symptoms, the use of vitamin B_6 or a multivitamin mineral formulation (Optivite) designed specifically for PMTS may provide some benefit. Third, patients who complain primarily of irritability can use progesterone suppositories. For patients

who complain primarily of depression, small doses of estrogen can be given during the luteal phase of the menstrual cycle. Fourth, when mastalgia is the primary complaint, bromocriptine may provide relief. Finally, when edema is present, diuretic therapy is beneficial.

Caught in the middle of this treatment dilemma is the PMTS sufferer. According to Keye (1985), medical treatments for PMTS can be divided into three major groups. The first group includes treatments that are designed to relieve specific symptoms without attempting to modify the underlying disease process. The next group consists of treatments that presumably correct what is hypothesized as the underlying pathophysiology of the disorder. The last group contains treatments that alter the normal ovulatory menstrual cycle. The product under investigation in this study falls into the first treatment category.

The purpose of this study is to determine the effectiveness of an analgesic, diuretic, antihistamine combination in the treatment of PMTS. At the present time there is no clear cut evidence for the effectiveness of any one treatment (Keye, 1985). That is because previous investigations have been compromised by various factors.

O'Brien (1835) suggested many factors that may impact PMTS studies such as, an inexact definition of PMTS, no objective parameters to measure in order to make a correct diagnosis, and the unknown cause of the disorder. However, the primary cause of the abundance of inadequate PMTS

research is the consistent failure to use placebos in drug trials when the high placebo response rate in PMTS (30%-80%) requires the inclusion of a placebo-control group (Smith and Youngkin, 1986). According to Steiner and Carroll (1977), most controlled studies report favorable results, whereas most placebo controlled studies fail to demonstrate drug/placebo differences or find placebo to be the superior treatment.

Other factors that influence research results are small sample sizes, studies too short in duration to validate the effectiveness of the treatment, an heterogeneous sample, and poor control over concomitant medications (Chakmakjian, 1983; and Harrison et al., 1985).

In the Handbook of Nonprescription Drugs (1982) it is stated that OTC drugs are intended to be used to treat symptoms of minor discomfort, illness or injury. The FDA has been involved since 1972 in a review of nonprescription drug products to ensure that they contain safe and effective ingredients and bear fully informative labeling. However, for most nonprescription drugs there need not be an affirmative demonstration that specific formulations of active and inactive ingredients are safe and effective (Handbook of Nonprescription Drugs, 1982). This is one of the many reasons that compelled this author to investigate the effectiveness of PMTS treatments more fully.

Other reasons that stimulated an interest in this area of research include:

1. Drug companies which manufacture PMTS products were supplying the Miscellaneous Internal Panel with results of in-house studies.
2. The Miscellaneous Internal Panel's report was designed to generate public comment.
3. There is no clear indication which drug should be given to treat this condition.
4. A drug company's promotion of a product that has yet to be proven effective is exploitative,and is taking advantage of women in a fragile condition, many of whom are afflicted with chemophilia, an attitude generated from drug company promotion of "a pill for every ill."

It is the hypothesis of this author that the active treatment in this study, which consists of 500 mg. acetaminophen, 25 mg. pamabrom, and 15 mg. pyrilamine maleate, is not effective in the treatment of PMTS, and at the very most, no more effective than a placebo.

CHAPTER III

METHODS AND PROCEDURES

This study investigated the effects of an over-the counter (OTC) product containing 500 mg. of acetaminophen, an analgesic; 25 mg. of pamabrom, a diuretic; and 15 mg. of pyrilamine maleate, an antihistamine, on symptoms associated with premenstrual syndrome. Both the active treatment and the placebo were supplied by Glenbrook Laboratories, a Division of Sterling Drug Inc. The methods and procedures were submitted to and approved by the Oklahoma State University Institutional Review Board.

A total of 58 females initially agreed to participate in this double-blind, cross-over design study which lasted two months. The subjects were required to orally ingest eight caplets per day of either the active treatment or placebo when the symptoms of PMTS first presented themselves or when the subjects could expect the symptoms with some certainty, and continue this regimen until the beginning of menses. The subjects completed a menstrual symptom questionnaire (MSQ) at the beginning, at cross-over, and at the conclusion of the study. Standardized statistical methods were used for analyses.

Selection of Subjects

The population for this study was menstruating women who experienced premenstrual discomfort. A convenience sample of 58 women was obtained as a result of women responding to newspaper ads in the local paper and announcements on numerous bulletin boards throughout the Stillwater community and the Oklahoma State University campus. Subjects were also recruited from a number of health classes at Oklahoma State University. Forty-four of the subjects actually produced data. Of those who dropped out of the study, eight of the subjects did not have severe enough symptoms to warrant treatment, five subjects moved out of town and out of touch, and one subject got pregnant.

In order to be selected for the study the subjects had to have documented PMTS based on the criteria established by Abraham (1980) for women who scored their symptoms using a menstrual symptom questionnaire (MSQ). Subjects with moderate or severe symptoms of PMTS according to their score on the MSQ were asked to participate in the study. Those who agreed were randomly assigned to one of two groups. One group received the placebo first and then crossed over to the active treatment while the second group received the active treatment first then crossed over to the placebo.

The ages of the subjects ranged from 17-42 years (mean 26.8). The weight of the subjects ranged from 90-228 pounds (mean 130.27). The number of pregnancies previously experienced by the subjects ranged from 0-3 (mean .66). The

length of the subjects menstrual cycles ranged from 20-34 days (mean 28.1). Twenty-four of the subjects were taking oral contraceptives while 20 were not taking the birth control pill.

Personal Data

Upon making contact with the investigator each subject was initially required to read and sign an informed consent for the testing procedure (see Appendix). Then each subject filled out an MSQ consisting of a brief personal history which included questions regarding age, height, weight, marital status, present contraception, previous treatment for PMTS, and length of menstrual cycle (see Appendix).

Also included on the form was a premenstrual symptom rating scale which yielded the baseline data that was used to screen subjects for participation in the study. Each subject was asked to evaluate her premenstrual symptoms for her last menstrual cycle. All subjects were also asked to grade the effects of PMTS on marital, familial, social and work-related activities during their last menstrual cycle (see Appendix). The forms were thoroughly explained by the investigator and questions were answered to the satisfaction of each of the subjects.

Data Collection

After completing the informed consent and the initial MSQ and agreeing to participate in the study, all of the

subjects were given instructions regarding the treatment protocol they were to follow for their next two menstrual cycles. For both of the test periods all of the subjects were asked to take eight caplets per day of whatever treatment they were receiving that month when symptoms of PMTS were present.

After completion of the treatment all of the subjects were asked to fill out a new premenstrual symptom rating scale. In addition, the subjects were asked if they followed the dosage recommendations and if there were any side effects while on the treatment. The same protocol was used for both test periods.

Instrumentation

The instrument used in this study to measure the presence of PMTS and the effect of the treatment on the symptoms of PMTS was a MSQ developed by Abraham (1980) (see Appendix). This MSQ was a modified form of a menstrual distress questionnaire developed by Moos (1968) and consisted of 19 items arranged into four subgroups. The four subgroups included: PMT-A, consisting of nervous tension, mood swings, irritability and anxiety; PMT-H, which included weight gain, swelling, breast tenderness and abdominal bloating; PMT-C, consisting of headache, craving for sweets, increased appetite, heart pounding, fatigue and dizziness; and PMT-D, which included depression, forgetfulness, crying, confusion and insomnia.

The symptoms were evaluated on a four-point scale which consisted of: 0 = none; 1 = mild - present but does not interfere with activities; 2 = moderate - present and interferes with familial, marital, social and work-related activities but is not disabling; and 3 = severe - disabling with marked decrease in performance and inability to function.

Statistical Treatment

This study was placebo-controlled, double-blind, and employed a cross-over research design. In this design each subject was allowed to act as her own control (Campbell and Stanley, 1963).

The data were analyzed using a 3 x 2 repeated measures analysis of variance with a trial factor at three levels (pre-test vs. active vs. placebo), and a grouping factor at two levels (birth control pill vs. no birth control pill). The following dependent variables were each analyzed separately: (1) total MSQ score; (2) PMT-A score; (3) PMT-H score; (4) PMT-C score; and (5) PMT-D score. All statistical tests were performed using the .05 level of significance. Statistical analysis was done through the Oklahoma State University Computer Center.

CHAPTER IV

RESULTS AND DISCUSSION

The purpose of this study was to determine if an over-the-counter (OTC) product consisting of 500 mg. of acetaminophen, 25 mg. of pamabrom and 15 mg. of pyrilamine maleate ameliorated the symptoms of PMTS in 44 subjects with documented PMTS according to their score on a menstrual symptom questionnaire (MSQ). The experimental design was a double-blind cross-over utilizing two groups, with each subject acting as their own control. The groups were controlled by administering a placebo.

All of the 44 subjects had documented the presence of their PMTS symptoms by completing a MSQ. All of the subjects rated their symptoms on the pre-test MSQ as moderate or severe according to the criteria established by Abraham (1980). At the time of the study none of the subjects were taking any other treatments for PMTS or any other OTC medications. No other attempts were made to control the general living habits of the subjects, except in the days immediately preceding menses, when late, irregular hours and alcohol were to be avoided in so far as possible.

Of the 58 subjects that began the study, 44 completed the study. Eight of the subjects did not have severe enough

symptoms to justify treatment, five of the subjects moved and dropped out of the study, and one became pregnant and dropped out of the study. Both the active treatment and the placebo were tolerated well by all subjects with the exception of three subjects who experienced side effects while on the active treatment. One subject reported lowered blood pressure and light headedness, one said she became groggy and thirsty, and one said she became very irritable and tired.

Results

The means and standard deviations by group (birth control pill vs. no birth control pill) and by condition (pre-test vs. active treatment vs. placebo) for the dependent variable of total MSQ score are given in Table I. The means and standard deviations by group and by condition for the other four dependent variables (PMT-A, PMT-H, PMT-C, PMT-D) are given in Tables II-V.

Results of Total MSQ Score Analysis

The results of the total MSQ score analysis by group and by condition are given in Table VI. There was a change in the total MSQ score at the .01 level of significance. A Newman-Keuls post hoc analysis was performed to determine the nature of the difference and a statistically significant difference was revealed between the pre-test MSQ score and

TABLE I

MEANS AND STANDARD DEVIATIONS FOR
TOTAL MSQ SCORE

	Birth Control Pill	No Birth Control Pill	All Subjects
Pretest	22.55 ± 6.95	26.29* ± 7.70	24.59
Active	24.75 ± 9.37	23.42 ± 11.58	24.02
Placebo	23.95 ± 10.39	20.25* ± 11.07	21.93

* 26.29 significantly different from 20.25

TABLE II

MEANS AND STANDARD DEVIATIONS FOR
PMT-A MSQ SCORE

	Birth Control Pill	No Birth Control Pill	All Subjects
Pretest	7.20 ± 2.19	7.92 ± 2.17	7.59*
Active	7.15 ± 2.58	6.88 ± 2.88	7.00
Placebo	6.90 ± 2.45	6.00 ± 3.04	6.41*

* 7.59 significantly different from 6.41

TABLE III

MEANS AND STANDARD DEVIATIONS FOR
PMT-H MSQ SCORE

	Birth Control Pill	No Birth Control Pill	All Subjects
Pretest	4.90 ± 2.29	6.21 ± 2.40	5.61
Active	5.80 ± 3.07	5.54 ± 2.78	5.66
Placebo	5.55 ± 2.67	4.71 ± 3.16	5.09

TABLE IV

MEANS AND STANDARD DEVIATIONS FOR
PMT-C MSQ SCORE

	Birth Control Pill	No Birth Control Pill	All Subjects
Pre-test	5.70 ± 2.49	6.88 ± 3.662	6.34
Active	6.35 ± 2.70	5.92 ± 3.67	6.11
Placebo	6.10 ± 3.74	5.38 ± 3.81	5.70

TABLE V

MEANS AND STANDARD DEVIATIONS FOR
PMT-D MSQ SCORE

	Birth Control Pill	No Birth Control Pill	All Subjects
Pre-test	4.75 ± 2.85	5.29 ± 2.94	5.05
Active	5.50 ± 2.91	5.04 ± 4.12	5.25
Placebo	5.40 ± 3.44	4.17 ± 3.63	4.73

TABLE VI

ANALYSIS OF VARIANCE FOR
TOTAL MSQ SCORE

Source	SS	d.f.	M.S.	F*
Pill group	6.07	1	6.07	0.03
Error	9290.90	42	221.21	—
Condition	137.22	2	68.61	2.21
Condition x pill group	315.40	2	157.70	5.07
Error	2612.04	84	31.10	--

* P<.01

the MSQ score obtained after the subjects took the placebo for the group of women not taking the birth control pill.

Results of MSQ Score Analysis
for PMT-A Subgroup

The results of the MSQ score analysis for the PMT-A subgroup by group and by condition are given in Table VII. There was a change in the PMT-A score at the .05 level of significance. A subsequent Newman-Keuls post hoc analysis revealed a statistically significant difference between the pre-test MSQ score and the MSQ score after the placebo was taken when the scores of both groups were combined.

Results of MSQ Score Analysis
for PMT-H Subgroup

The results of the MSQ score analysis for the PMT-H subgroup by group and by condition are given in Table VIII. There was a change in the PMT-H score at the .05 level of significance for the group of women who were not taking the birth control pill. However, a Newman-Keuls showed no pairs of means to be significantly different from one another.

Results of MSQ Score Analysis
for PMT-C Subgroup

The results of the MSQ score analysis for the PMT-C subgroup by group and by condition are given in Table IX. There was a change in the PMT-C score at the .05 level of

TABLE VII

ANALYSIS OF VARIANCE FOR
PMT-A MSQ SCORE

Source	SS	d.f.	M.S.	F*
Pill group	0.76	1	0.76	0.006
Error	547.90	42	13.05	--
Condition	26.80	2	13.40	3.83
Condition x pill group	14.50	2	7.25	2.07
Error	294.11	84	3.50	--

* P<.01

TABLE VIII

ANALYSIS OF VARIANCE FOR
PMT-H MSQ SCORE

Source	SS	d.f.	M.S.	F*
Pill group	0.1666	1	0.16	0.01
Error	685.90	42	16.33	--
Condition	7.09	2	3.55	1.12
Condition x pill group	26.97	2	13.49	4.24
Error	266.92	84	3.18	--

* P<.05

TABLE IX

ANALYSIS OF VARIANCE FOR
PMT-C MSQ SCORE

Source	SS	d.f.	M.S.	F*
Pill group	0.001	1	0.001	0.00
Error	1171.961	42	27.904	--
Condtion	7.025	2	3.512	1.00
Conditoin x pill group	22.843	2	11.421	3.26
Error	294.672	84	3.508	--

* P<.05

significance for the group of women who were not taking the birth control pill, but a subsequent Newman-Keuls revealed no pairs of means to be significantly different from one another.

Results of MSQ Score Analysis for PMT-D Subgroup

The results of the MSQ score analysis for the PMT-D subgroup by group and by condition are given in Table X. There was no change in the PMT-D score at the .05 level of significance.

TABLE X

ANALYSIS OF VARIANCE FOR
PMT-D MSQ SCORE

Source	SS	d.f.	M.S.	F*
Pill group	4.809	1	4.809	0.17
Error	1189.517	42	28.322	--
Condition	5.186	2	2.593	0.90
Condition x pill group	17.277	2	8.638	2.98
Error	243.283	84	2.896	--

* No significance

Discussion of Results

The interaction between the active treatment in this study and the symptoms of PMTS is not clearly understood at the present time. This is the first study to investigate acetaminophen, pamabrom, and pyrilamine maleate in combination. Previous studies have only investigated the effects of pamabrom and pyrilamine maleate individually and in combination, and have produced conflicting results. In this study, even though statistically significant differences were seen in a couple of areas, the differences were so small that no practical beneficial outcome was derived.

The results of this study indicated statistically significant changes in PMTS scores in four different areas. Three of the changes occurred in the group of women who were not taking oral contraceptives. For these women there was a reduction in their total MSQ score, the MSQ score for the PMT-H subgroup, and the MSQ score for the PMT-C subgroup. However, the reduction of their MSQ scores was not large enough to reflect any relief of symptoms of PMTS. In other words, the women in this study suffer from what has been described as moderate-to-severe PMTS according to their MSQ scores (Abraham 1980) and the observed reduction in the MSQ scores indicated the subjects still had noticeable symptoms. Also, it must be noted that all of the statistically significant changes in MSQ scores occurred between the pre-test and the placebo cycle. This is consistent with the extremely high placebo response rate, 30%-80%, seen in studies of PMTS treatment (Smith and Youngkin 1986).

The other statistically significant change seen in this study occurred between the pre-test and the placebo cycle for the PMT-A subgroup for both groups of subjects combined. Once again, even though the change in the MSQ score was statistically significant, no practical benefit was derived from the limited symptom reduction because the women still had noticeable symptoms of PMTS.

It is difficult to compare the results of this study to other studies involving PMTS treatments for a number of rea-

sons. First, no other study has been done using the particular combination investigated in this study, which consists of 500 mg. of acetaminophen, 25 mg. of pamabrom, and 15 mg. of pyrilamine maleate. Second, the instrument used to measure the presence and severity of PMTS varies from study to study. Finally, many of the past studies were open trials rather than placebo-controlled studies.

The effectiveness of acetaminophen in the relief of premenstrual discomfort by itself or in combination with other products has not been determined because it has not been investigated for that particular purpose. Nevertheless, acetaminophen has been commonly used for menstrual pain in the past and has been rated as safe when taken in recommended doses (Federal Register 1977).

The Wisconsin Study (1978) investigated the effects of 50 mg. of pamabrom on symptoms of PMTS and found that it reduced the symptoms of headache, depression and finger swelling. In contrast, Rogers (1964) pointed out that diuretics frequently failed to relieve headache, tension and nervousness (in Wisconsin Study 1978). Harrison, Sharpe and Endicott (1985) reviewed five controlled studies of diuretics and only two demonstrated a beneficial effect. It should also be mentioned that the blind nature of any trial using diuretics is questionable because the increased urination caused by the active treatment provides clues as to the nature of the treatment.

The Wisconsin Study (1978) also investigated the effects of 25 mg. of pyrilamine maleate on PMTS symptoms and discovered it reduced tension, irritability, and cramps. Another study by McColl and Durkin (1981) found pyrilamine maleate to be effective in reducing the intensity of cramps, backache, anxiety, and swelling. These are the only studies that have been done involving pyrilamine maleate by itself.

The effect of 50 mg. of pamabrom and 25 mg. of pyrilamine maleate in combination on symptoms of PMTS has also been investigated. It has been suggested that this combination produced an enhanced clinical response on breast tenderness, swelling of the abdomen, cramps, tension, swelling of the fingers and ankles, headache, depression, and irritability (Wisconsin Study, 1978).

Despite the differences in the selection of subjects, type of experimental treatment, and the type of instrument used to measure the presence and severity of PMTS, all of the aforementioned studies that indicated a reduction in symptoms of PMTS had something in common. Even though some reduction in symptoms of PMTS was observed, and those reductions were statistically significant, none of the studies revealed a reduction great enough to have any real practical benefit for women with PMTS.

There are a number of complicating factors that make it difficult to interpret the results of this study and other studies involving the investigation of treatments for PMTS. One primary area of concern in PMTS research which has made

interpretation of results very difficult is the lack of an objective instrument for assessing the condition. Measurement of body dimensions, blood changes, and weight have been found to be of no value in diagnosing and evaluating symptoms of PMTS and responses to therapy (O'Brien, Faratian, Gaspar et al., 1983). Self-assessment of mood is the most widely used method at present and may consist of a daily menstrual chart, the Moos MDQ (1968), or Abraham's MSQ (1980). According to O'Brien (1985), the menstrual chart is useful in assessing the character and timing of symptoms, but is of no benefit in assessing the severity of symptoms and consequently is only useful for diagnosis. The other two methods are more widely used in research because they reflect both the timing and the degree of disability.

Both the Moos MDQ (1968) and the Abraham MSQ (1980) are retrospective questionnaires. It has been suggested by a number of researchers (McCance, Ruff and Widdowson, 1937; Ablanalp, Donnelly and Rose, 1978; Sampson and Prescott, 1981) that retrospective symptom ratings are not generally validated by daily prospective ratings, but in fact, overestimate symptoms. A study by Endicott and Halbreich (1982) compared 48 women's retrospective reports of premenstrual depression with their rating of depression in their daily menstrual diary and found the women described the symptoms as much less severe in their daily reports than they did in their retrospective report. On the other hand, Moos (1968) and Rouse (1978) found that when a retrospectively adminis-

tered questionnaire was completed by women at different phases of their most recent menstrual cycle, no phase effect on their symptom scores was obtained.

Abraham's MSQ (1980) was utilized in this study and is a modified version of the Moos MDQ (1968). Rubinow and Roy-Byrne (1984) evaluated both questionnaires and found both lacking in one way or another. The Moos MDQ (1968), a 47-item checklist, focused largely on physical symptoms with the psychological, emotional, and behavioral symptoms being less extensively cataloged. The lack of specific inclusion and exclusion criteria limited the ability of the MDQ to translate changes in mood and behavior into useful diagnostic categories (Rubinow and Roy-Byrne, 1984). Abraham's MSQ (1980) consists of a 19-item symptom checklist divided into four subgroups. Unfortunately, since the scale only contained 19 items and was not constructed by using standardized psychometric procedures which would ensure internal consistency, reliability, reduction of redundancy, and cohesiveness of subgroups, the sensitivity and specificity of this construct was seen as questionable (Rubinow and Roy-Byrne, 1984). So, at the present time there is no universally accepted method of objectively evaluating syndromes that more frequently consist of internally experienced symptoms than objective behavioral signs, and consequently, interpretation of results is very difficult.

A number of other factors which have been cited in the literature and make it difficult to meaningfully interpret

the results of this study are as follows: (1) the etiology of PMTS is no closer to being understood than when it was first described by Frank (1931), and there remains no consistent data on the physiologic, biochemical and endocrine changes that occur during the premenstrual phase (O'Brien, 1985); (2) PMTS has never been adequately defined, which has made it impossible to delineate specific parameters to measure to determine the presence and severity of PMTS; (3) there is considerable diversity in severity and variability of PMTS symptoms from patient-to-patient and in the same patient from month-to-month (Chakmakjian, 1983); (4) the placebo response rate has been chronicled as being between 30%-80% in subjects with PMTS (Smith and Youngkin, 1986) and is partially the result of inadequate instruments for determining the presence and severity of PMTS symptoms; and (5) a lack of control over lifestyle variables such as diet, exercise, stress, rest, and the use of drugs also makes it difficult to interpret these results.

CHAPTER V

SUMMARY, FINDINGS, CONCLUSION AND RECOMMENDATIONS

Summary

Ever since Frank (1931) first described a group of symptoms occurring cyclically during the premenstruum, women suffering from what has come to be called PMTS, have been inundated by treatment options promoted by physicians and pharmaceutical companies. Over 300 therapies have been promoted for providing relief from the disruptive and at times disabling symptoms of PMTS, yet the effectiveness of these therapies has never been substantiated.

In recent years PMTS has become a recognized clinical entity affecting a large portion of the female population. A reflection of the increasing concern about PMTS is the existence of more than 200 free-standing clinics and referral or information sources directed at PMTS sufferers within the United States (True, Goodner and Burns, 1985). However, women seeking advice or treatment for PMTS must be acutely aware of false claims and dubious schemes in the marketplace. OTC products which were once marketed to relieve menstrual cramps are now described as helpful for PMTS. The medication has simply been repackaged, relabeled, or in some

cases, given a new title. These products may diminish cramps, but are largely ineffective in treating PMTS (PMS Access, 1986).

OTC drugs are intended to be used to treat symptoms of minor discomfort or illness. Usually, their aim is to make the consumer more comfortable as long as the condition lasts, although they include some prophylactic ingredients and some ingredients capable of treating and curing certain minor conditions (Gilbertson, 1982). However, according to O'Brien (1982), it is important to realize that one drug does not cure all patients or symptoms. Advertisements for OTC products often claim that this is the case. They suggest their product provides relief for all symptoms of PMTS.

So, how can a PMTS sufferer be sure that an OTC medication will work or that it is safe? The Food and Drug Administration (FDA) has been involved since 1972 in a review of nonprescription drug products to ensure they contain safe and effective ingredients and bear fully informative labeling. For most nonprescription drugs there need not be an affirmative demonstration that specific formulations of active and inactive ingredients are safe and effective (Gilbertson, 1982). This loophole is one of the factors that motivated this researcher to investigate the effectiveness of OTC products for PMTS.

Gilbertson (1982) described the FDA's OTC drug review program as a three-phase rulemaking process culminating in the establishment of standards for the different nonpre-

scription therapeutic drug categories. The first phase of the process extended over a period of almost ten years and was accomplished by an advisory review panel of non-FDA experts. The panel reviewed over 14,000 volumes of data submitted largely by manufacturers, but also by concerned consumers, pharmacists and other interested parties. The panel reviewed the drugs to determine whether their ingredients could be generally recognized as safe and effective for use in self-treatment. They were also charged with reviewing claims and recommending appropriate labeling, including therapeutic indications, dosage instructions, and warnings about side effects and preventing misuse.

According to the terms of the review, the panel classified ingredients as Category I, II or III. Category I drugs are generally recognized as safe and effective for the claimed therapeutic condition. Category II drugs are not generally recognized as safe and effective or have unacceptable indications. Category III drugs have insufficient data available to permit final classification.

The panel's findings were reported in the Federal Register as an Advanced Notice of Proposed Rulemaking and public comment was invited. At the present time the FDA is in the second phase of the OTC drug review, which involves the FDA's review of the ingredients in each class of drugs, based on the outside panel's findings, on public comment, and on new data that have become available. This opportunity to provide input into the FDA's rulemaking process was

another factor that motivated this researcher to investigate OTC products for PMTS.

It appears our country is afflicted with widespread chemophilia, a love of chemicals. It would seem people are less concerned with modifying behaviors than with finding a miracle pill to make them feel better. Pharmaceutical companies are partially responsible for this attitude because they have successfully promoted the idea that there is a pill for every ill, or a chemical solution to every physical, emotional, or social problem. These pharmaceutical companies invest a significant proportion of their profits on advertising to encourage the use of both OTC and prescription drugs.

With respect to OTC menstrual products, the manufacturers market their products based on unsubstantiated claims of effectiveness, which women, desperate for relief, believe. According to Keye (1985), women with mild premenstrual symptoms usually do not report any therapeutic effect from OTC drugs. In some cases a product may provide temporary relief, but rarely the consistent, long-term relief that would enable the PMTS sufferer to exert some measure of control over her life.

With all the dubiety surrounding PMTS treatment, this investigator questioned how pharmaceutical companies could claim their products relieved symptoms of PMTS when no product had been proven to be completely successful in alleviating these symptoms. With knowledge of the FDA's review pro-

cess the investigator now understands that manufacturers are at their own risk and buyers must beware until data are produced that either confirm or discount the claims being made for OTC products for PMTS. Therefore, the purpose of this study was to determine if the oral ingestion of eight caplets daily, when PMTS symptoms were present, of a product containing 500 mg. of acetaminophen, 25 mg. of pamabrom, and 15 mg. of pyrilamine maleate, would relieve symptoms of PMTS.

This study was conducted as a double-blind cross-over, using a 3 x 2 repeated measures analysis of variance with a trial factor at three levels (pre-test vs. active treatment vs. placebo), and a grouping factor at two levels (birth control pill vs. no pill).

Findings

Based on the stated hypotheses and the limits of the study, the following findings were made:

1. The oral ingestion of eight caplets per day when PMTS symptoms were present had a statistically significant effect at the .01 level on the total MSQ score in the group of subjects who were not using oral contraceptives when the pre-test MSQ score was compared to the MSQ score after the placebo was administered. Even though the difference was statistically significant, it had no real

practical significance, and was attributed to the high placebo response rate associated with PMTS.

2. The oral ingestion of eight caplets per day when PMTS symptoms were present had a statistically significant effect at the .05 level on the MSQ score for the PMT-A subgroup when comparing the pre-test PMT-A score for all subjects with the PMT-A score for all subjects after the placebo had been administered. Even though the difference was statistically significant it had no real practical significance due to the fact that the difference occurred after the administration of the placebo.
3. The oral ingestion of eight caplets per day when PMTS symptoms were present had a statistically significant effect at the .05 level on the MSQ score for the PMT-H subgroup in the group of subjects who were not using oral contraceptives. However, a subsequent Newman-Keuls post hoc analysis revealed no pairs of means to be significantly different from one another.
4. The oral ingestion of eight caplets per day when PMTS symptoms were present had a statistically significant effect at the .05 level on the MSQ score for the PMT-C subgroup in the group of subjects who were not using oral contraceptives. A Newman-Keuls post hoc analysis revealed no pairs

of means were significantly different from one another.

5. The oral ingestion of eight caplets per day when PMTS symptoms were present had no significant effect when comparing the group of women using oral contraceptives and the group not using oral contraceptives.

Conclusion

Based on the results of this study, this investigator concluded that the active treatment in this study does not provide relief for women who have moderate-to-severe PMTS.

Recommendations

It would seem that the status of the OTC drug under investigation needs to be reclassified from Category I to Category II. The results of this study indicated that the active treatment in this study, which consists of 500 mg. of acetaminophen, 25 mg. of pamabrom, and 15 mg. of pyrilamine maleate, and is presently being marketed as an OTC medication for PMTS, does not provide effective relief for the symptoms of PMTS. However, it should also be noted that other studies which investigated similar products (Wisconsin Study, 1978; McColl and Durkin, 1981) produced results which indicated pamabrom and pyrilamine maleate by themselves, and in combination, reduced the symptoms of PMTS.

The reasons for the conflicting evidence that continues to come out of studies involving PMTS treatments are many. This particular area of research is fraught with methodological barriers and because of this no one is able to offer effective treatment at this time. The methodological flaws that plague PMTS research form the basis for recommendations for future research.

First and foremost, the underlying cause of PMTS must be discovered before effective treatment can be offered. Once the cause is determined then an exact definition for PMTS can be developed and an objective instrument for measuring the presence and severity of PMTS symptoms can be constructed. If these three recommendations can be accomplished, much of the confusion surrounding PMTS will be resolved.

However, until the time comes that a cause, a definition, and an objective instrument can be developed, the following recommendations would improve research in this area:

1. Most importantly, future studies must use placebo-controlled, double-blind formats in all research into the efficacy of drugs for the symptoms of PMTS.
2. The use of small, heterogeneous sample sizes must be avoided.
3. The length of the studies must be increased to at least six consecutive months to reduce the impact

of the variability of symptoms from month-to-month.

4. Control over extraneous variables, such as diet, stress, exercise, and other drugs needs to be tightened to reduce the impact on the experimental treatment being investigated.

Finally, from a practical perspective, following are a number of recommendations from Harrison, Sharpe and Endicott (1985) for those women who continue to be frustrated by the PMTS treatment dilemma:

1. Initial therapeutic management should consist of education and support along with a thorough physical and psychological exam.
2. A regular menstrual cycle calendar/diary should be kept so activities can be planned around the premenstrual phase and also so that understanding can be increased regarding specific symptoms.
3. Nutritional evaluation and counseling are necessary so troublesome foods that contain salt, sugar and caffeine can be avoided.
4. For particularly persistent or severe symptoms, pharmacologic treatment is recommended.

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APPENDIX

INFORMED CONSENT FORM

By signing this document you are agreeing to participate in an experimental research study. The purpose of this research is to determine the effectiveness of an over-the-counter product in the treatment of premenstrual distress. If you qualify and agree to participate in the study you are advised that the study will take place over two consecutive months.

To qualify for the study you will initially fill out a Menstrual Symptom Questionnaire (MSQ) to determine the presence and severity of symptoms you have that are associated with premenstrual distress. If your MSQ score meets the established criteria for inclusion in this study, you will then be randomly assigned to one of two groups. Both groups will receive two different treatments, an over-the-counter product and a placebo in a double-blind crossover fashion. Double-blind means neither you or the investigator will know which of the two treatments you will be receiving. Crossover means you will receive the over-the-counter product one month and the placebo one month.

If you are in one of these treatment groups you will be asked to begin taking the treatment on day one of the onset of premenstrual distress and continue taking the recommended daily dosage until the onset of menses. The recommended daily dosage is two caplets with water every four hours with a maximum daily dosage of eight caplets per day. For this study you will take the maximum daily dosage of eight caplets per day.

After the treatment period is over you will be asked to fill out a MSQ to evaluate the effect of the treatment on your premenstrual symptoms. This procedure will take place over two consecutive months.

The active treatment in this study is a commercial product whose trademark is to remain confidential to the investigator. This treatment, which is available as an over-the-counter product, consists of 500 mg. of acetaminophen, an aspirin-like substance used for relief of pain; 25 mg. of pamabrom, a diuretic that relieves water retention and pyrilamine maleate, an antihistamine that has pain-dulling properties. The other treatment to be used in this study is a placebo containing an inert substance, lactose, a milk sugar.

The Food and Drug Administration's Advisory Review Panel on Over-the-Counter Miscellaneous Internal Drug Products reviewed data on over-the-counter menstrual drug products containing a diuretic (pamabrom), an antihistamine (pyrilamine maleate) and an analgesic (acetaminophen). The Panel classified the combination, as well as the individual

ingredients, as Category I for relieving symptoms of premenstrual syndrome. A Category I designation by the Panel indicates conditions under which over-the-counter menstrual drug products are generally recognized as safe and effective and are not misbranded. However, you should be advised that even though these products have been labeled as safe and effective by the Food and Drug Administration, there may be side effects.

The Panel found acetaminophen relatively free of adverse effects and the only known contraindication to the use of acetaminophen is hypersensitivity to the drug. The side effects of antihistamines may include mild sedation, listlessness, irritability and loss of appetite. Pamabrom has shown no evidence of significant toxicity or adverse reactions since it was approved for over-the-counter marketing in 1952.

Your participation in this experiment is voluntary and confidential and you may withdraw without prejudice at any time. You will not receive any compensation for your participation in this experiment and you will be responsible for any medical expenses you may incur.

If you experience any physical discomfort as a result of your participation in this experiment, please contact Dr. Alice Gambill or Dr. Donald Cooper, physicians at the Oklahoma State University Student health Center. Dr. Gambill and Dr. Cooper will be available from 8am-5pm, Monday through Friday. You can also contact Dr. Gambill by phone at 624-7019 and Dr. Cooper at 624-7031.

If any problems occur between the hours of 5pm-8am or on weekends, you can contact the Emergency Room at the Student Health Center and tell the staff you are part of an experiment involving Dr. Gambill and Dr. Cooper and they will contact the physician for you.

If you have any questions regarding your participation in this study please feel free to ask the investigator now or at any time during the experiment.

_____ _____

Subject Date Investigator Date

_____

Witness Date

MENSTRUAL SYMPTOM QUESTIONNAIRE (MSQ)

Name: _____

Age: _____ Height: _____ Weight: _____

Marital Status: _____ Single _____ Married _____ Divorced _____ Widowed

Present Contraception: _____ None _____ Pill _____ IUD _____ Other

History of taking contraceptive pills: ____Yes ____No If yes, months ago: _____

For how long: _____months. Number of Pregnancies: _____ Children: _____

How long have you suffered from premenstrual complaints: _____ years

Previous treatment: _____None _____Sedative _____Antidepressant

_____Water pills _____Birth control pills _____Progesterone _____Bromocriptine

_____Primrose oil Other (specify): _____

Duration of previous treatment: _____ months. Last treatment _____ months ago

Response to treatment: _____Excellent _____Good _____None _____Worse

Have you ever been diagnosed as having endometriosis? _____Yes _____No

Are you presently taking any other prescription or over-the-counter medications?

_____Yes _____No _____If yes, specify: _____

Your last period started _____ (date). Your last period lasted _____ days.

Your last menstrual cycle was _____ days long. Your last period was:

_____Light _____Moderate _____Heavy

Occupation: _____

Grading of Symptoms and Grading of Effects of PMT on Performance

0 - No Effect.

1 - Mild - Present, but does not interfere with performance at home, at work and during social activities. Not noticeable by others.

2 - Moderate - Interferes with familial, marital, social and work-related activities. Able to function without medication at a lower level of performance. Noticeable by others.

3 - Severe - Disabling. Marked interference with and complete disruption of familial, marital, social and work-related activities. Unable to function without medication. Very noticeable by others.

Grade Your Symptoms For Last Menstrual Cycle Only

SYMPTOMS	Week After Period	Week Before Period
Nervous tension	_____	_____
Mood swings	_____	_____
Irritability	_____	_____
Anxiety	_____	_____
	Total_____	Total_____
Weight Gain	_____	_____
Swelling of extremities	_____	_____
Breast tenderness	_____	_____
Abdominal bloating	_____	_____
	Total_____	Total_____
Headache	_____	_____
Craving for sweets	_____	_____
Increased appetite	_____	_____
Heart pounding	_____	_____
Fatigue	_____	_____
Dizziness or fainting	_____	_____
	Total_____	Total_____
Depression	_____	_____
Forgetfulness	_____	_____
Crying	_____	_____
Confusion	_____	_____
Insomnia	_____	_____
	Total_____	Total_____
TOTAL MSQ SCORE	_____	_____

Grade the Effects of PMT on Performance For Last Menstrual Cycle Only

ACTIVITY	Week After Period	Week Before Period
Marital	_____	_____
Familial	_____	_____
Social	_____	_____
Work-Related	_____	_____

Grade the Effects of the Treatment on Performance for Last Menstrual Cycle Only

-1 = Worse
0 = No effect
1 = Slight improvement
2 = Moderate improvement
3 = Marked improvement

ACTIVITY	Week After Period	Week Before Period
Marital	_____	_____
Familial	_____	_____
Social	_____	_____
Work-Related	_____	_____

Using the above scale how would you grade the effects of the treatment on the relief of the symptoms of menstrual distress _____.

Did you follow the dosage recommendations:

_____Never _____Rarely
_____Most of the time _____Always

Any side effects while on the treatment? (specify)

_____

_____

_____

_____

_____

_____

Comments: _____

_____

_____

_____

_____

_____

_____

VITA

Paul A. Finnicum

Candidate for the Degree of

Doctor of Education

Thesis: THE EFFECT OF AN OVER-THE-COUNTER PRODUCT IN THE TREATMENT OF PREMENSTRUAL TENSION SYNDROMES

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