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PROBLEMS FACED IN CONDUCTING CLINICAL TRIALS OF DRUGS IN PMS

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Abstract- Introduction: Premenstrual syndrome is a psychoneuroendocrine disorder of unknown etiology. Even after > 80 years of its 1st description, its definition, presenting patterns , diagnostic plan and treatment modalities are surrounded by many questions and controversies. This results in a large number of studies with different criteria's and methodologies so that their results are not comparable.
Objective : To descries variability in opinions about PMS and highlight problems encountered in designing and conduct of clinical trials of various drugs in premenstrual syndrome.
Method : The literature available in journals since inception of the term Premenstrual syndrome was reviewed. Variability in opinions of different workers regarding definition of PMS, days of premenstruum, diagnostic parameters was recorded and analysed. The methodological constraints in clinical trials of PMS due to lack of consensus among workers are mentioned and some corrective measures are suggested.
Results : There is no consensus among workers regarding different aspects of premenstrual syndrome resulting in difficulties in designing and conduct of clinical trials in PMS.
Conclusion : The authorities and organizations involved in research on PMS must frame standard guidelines for acceptable criteria and trial designs. So that comparative study of different trials becomes possible. Large multicentric trials in identical groups of population at same period of time by uniformly trained investigators are another alternative. Further research to elucidate exact etiopathogenesis and treatment guidelines is essential.
Keywords- Premenstrual syndrome, Clinical trials, Blinding, Randomization, Bias

Introduction

The term' Premenstrual syndrome' has been raising controversies since its inception. Its definition, symptomatology, etiology, diagnosis and treatment all are surrounded by many questions. The same is true about designing and conduct of clinical trials in PMS. This article describe variability in opinions about definition, presentation patterns, diagnostic methods & highlights methodological problems encountered in designing and conduct of clinical trials in PMS, which limit their usefulness and scope. Authorities and organizations involved in PMS research must develop a consensus statement regarding various methodological issues, so that comparative evaluation of different treatment modalities becomes possible.

Definition

Definition of PMS has changed many times. This menstrual related disorder was initially described as ' a state of indescribable tension' [1] and ' a cyclically recurring mood disorder'[2]. Later the term expanded to encompass recurrent *physical, psychological and emotional symptoms, not due to any organic disease* [3]. The term 'Premenstrual dysphoric disorder' (PMDD) emphasizing more than severe mood related symptoms than somatic symptoms was enlisted in appendix of DSM IV (diagnostic & statistical manual- IV ed.) [4] with an aim to develop systematic diagnostic criteria. But it has narrow focus, as women with predominant anxiety related or physical symptoms are excluded [5]. Controversy exists about days of menstrual cycle constituting premenstrual [6-9]. Whether it is 4 days before & after onset of menstruation or 6 days before & 2 days after manstruation is not clearly known. Going by the name Pre- menstrual the symptoms must disappear at onset of menstrual bleeding or it should be better called 'pre-menstrual syndrome' [10] a term which also falls short in including symptoms occurring at midcycle [11- 13], menarche and menopause [14]. Although there are many different definitions of PMS, but the essence of all definitions is periodicity and the relationship between symptoms and the time of onset of menstruation [15].

Currently the most common definition being followed describe PMS as ' a group of menstrual related , chronic, cyclical disorder manifested by emotional and physical symptoms in 2nd part of menstrual cycle which subside after beginning of menstrual period' [16].

Variability of presentation

- Premenstrual syndrome comprises of a large number (> 150) of affective, autonomic, behavioural, cognitive, central, dermatological, fluid/electrolyte related, neurovegetative and pain related symptoms.[17].
- A particular patient may present with any constellation of symptoms. The most commonly reported symptoms , irritability (84%), anxiety (83%) and mood liability(77%) are stable and consistent across cycles which justifies their use as outcome measures in determining the course of syndrome or efficacy of therapeutic interventions [18] .
- PMDD patients have individual- specific symptom patterns, stable and replicable across cycles. Most common and reproducible symptoms in PMDD also are anxiety, irritability and mood liability[18].
- Symptom severity is determined by highly subjective factors like degree of impairment or incapacitation caused in the form of marital discord, baby battering, poor work performance, increased accident proneness, criminal behaviour & suicidal ideation etc.
- Four different patterns of occurrence of symptoms in relation to menstrual cycle are reported[19]. Symptoms in some patients occur only for few days in late luteal phase or gradually increase in severity throughout the luteal phase to disappear abruptly at onset of menstruation or continue into early follicular phase of next cycle in others. Few patients complain of symptoms around time of ovulation also.

Difficulty in diagnosis & consequent need of special questionnaires:

Diagnosis of PMS has always been troublesome ,as no biochemical markers are available for objective diagnosis because of lack of consensus on etiopathogenic basis. 3 key elements considered essential for diagnosing PMS are ; a symptom complex consistent with diagnosis, a luteal phase pattern and symptom severity sufficient to disrupt patients' normal daily routine [20].

American college of Obstetric and gynaecology (ACOG) recommends presence of at least one psychological or physical symptom causing significant impairment and a 30% increase in symptoms score from days 5 to 10 as compared with 6 days interval before menses , documented on daily symptom diary for at least 2 consecutive cycles, to be diagnostic of moderate to severe PMS[21]. PMDD, the more severe form of PMS requires presence of at least 5 symptoms (4 of which are affective) with a rating of severe to extreme on at least 2 premenstrual days and a rating of minimal or absent postmenstrual [22]. With onset of menstrual bleeding serving as the only fixed point in cycle, patients may not recall symptoms occurring at other times during the cycle. Thus daily recording of symptoms is indispensible part of PMS diagnostic plan.

For prospective daily charting and rating of symptoms numerous 'questionnaires', 'research diagnostic criteria', 'visual analogue scales' and 'daily diaries' had been devised in past [9, 10,17 & 23-28]. Existence of 65 such questionnaires or scales has been confirmed [29] But none of them is flawless. Some questionnaires had faulty normative sample, others are too short or too elaborate. While brief questionnaires tend to exclude many patients actually suffering from the disease, the longer ones have poor patient compliance as major limitation due to time constraints Patient compliance with daily symptom recording is especially poor during symptom free period(proliferative phase) of cycle . Hence fall in symptom score from luteal to proliferative phase is difficult to document. Further daily diaries or calendars with self rating scales from (0-3) or even (0-4) become too complicated to be followed by patients of average intelligence.

Unfortunately, inconsistent acknowledgement of > 150 symptoms, occurring in different patterns in relation to menstrual cycle, coupled with use of highly subjective parameters for assessing symptom severity makes the diagnosis of PMS a real challenge.

Currently the diagnostic plan commonly being followed is ; a detailed history of patient (to ascertain ovulatory nature of cycles and to rule out other psychiatric / gynaecological / medical diseases) followed by prospective, daily charting and rating of symptoms by patient for at least 2 months (to document fall in symptom score from luteal to proliferative phase). Symptoms of sufficient severity during last week of luteal phase, beginning to remit at onset of menstruation and being completely absent 1 week thereafter confirm the diagnosis of PMS & rules out premenstrual exacerbation of other psychiatric/ somatic disorders.

Methodological issues and design consideration

Framing trial aim: - A precise aim is the first requirement of every clinical trial. Aim of treatment in PMS is either to suppress symptoms or ovulation or to correct putative etiological defect. But in PMS variable symptom constellations, impaired future reproducibility of patients with ovulation suppressants and incompletely understood etiology are problems in framing aim of clinical trial.

Trial Design: - Prospective, randomized, double blind, placebo controlled and cross over design is the most acceptable trial design for PMS. Difficulties are encountered in PMS trials at following steps;

1. Patient population and enrolment

Patients with comorbid physical or psychiatric disorders are usually excluded from the trials, although these are frequently exacerbated premenstrual [30]. Hence comorbidity remains an important unstudied aspect of PMS [31].

Prospective charting of symptoms for 1st 2 months is essential for diagnosing PMS and ascertaining symptom stability across cycles. Selective population which can fill up performs can be included in trials of PMS. Illiterate subjects are practically unable to participate in such trials. In a country like India with low literacy rate especially in rural areas, it is feared that patients participating in trials of PMS are not true representatives of the whole female population of the country making it

difficult to assess the effect of lack of education and low socioeconomic status on incidence of PMS.

2. Randomization and double blinding

During random allocation of patients to various treatment groups e.g., by using computer devised numbers, a patient with predominantly physical symptoms at baseline may fall in a group receiving drugs with known predominant effect on behavioural symptoms or vice versa. In such a situation investigator might have an urge to shift the patient to other group, which will bias the results. To remove investigators' bias, if a neutral person steps in to randomly allocate the patients to different treatment groups, the lack of patients' faith in this unfamiliar person may have a negative subjective influence on results.

Blinding faces problems in PMS as a patient suffering from multiple symptoms of such severity as to disrupt her normal life , may insist on knowing which drug is being prescribed for which symptom. If it is disclosed, the results are likely to be biased if not, patients' compliance with treatment regimen may be poor.

3. Placebo control

In widely accepted placebo controlled design, administration of supposedly inactive drug to patients with sufficiently severe symptoms seems unethical.

4. Cross over design

In crossover design longer duration of trial affecting patients' compliance is another limiting factor. A patient is required to fill daily symptom charts or diaries for 2 cycles to record baseline symptoms and for at least 1 cycle each to record the effect of placebo and test drug. Requirement of daily recording and rating of symptoms by patients for minimum 4 months continuously increases noncompliance and dropout rate. Moreover there are chances of natural remission or relapse of disease during this period leading to false positive or negative results respectively.

5. Logistics and cost

Longer duration of study increases the cost incurred. If a parallel group design is selected as an alternative, the homogenicity is lost because the severity of symptoms or degree of improvement with a drug felt by different patient can not be expected to be same.

Multicentric trials need uniformly trained investigators, equipment and monitoring, so are expected to be costlier.

Summary

Conducting clinical trials in patients of PMS has many methodological constraints. In the absence of knowledge of precise etio pathogenesis and bio-chemical markers, framing the aim and designing the methodology of trial in PMS becomes difficult . The non-compliance, cost, bias, ethical issues further complicate it. It is recommended that a consensus statement should be reached about the trial design, methodology, inclusion and exclusion criteria, and scale/ questionnaire to be used , because comparative study of various trials could yield fruitful results only if the above mentioned criteria are identical. As group size also needs to be optimum for drawing statistical conclusions , in coming time clinical trials for PMS should be conducted as large, well controlled multicentric trials at same period of time, in identical populations so that sociodemographic features do not alter the results obtained. Further evidence – based information about treatments and underlying mechanisms remains essential for increasing scientific understanding of the disorder and relieving the distress that it causes.

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