The efficacy and safety of Clomipramine Hydrochloride versus Dapoxetine Hydrochloride in Married Heterosexual Men with Premature Ejaculation: A Pragmatic, Randomized Controlled Trial

Debanjan Mandal

Dissertation submitted to The Tamil Nadu Dr. MGR Medical University, in part fulfilment of the requirement for MD Branch XVIII Psychiatry Final Examination to be held in May 2018

CERTIFICATE

This is to certify that the dissertation titled "The efficacy and safety of Clomipramine Hydrochloride versus Dapoxetine Hydrochloride in Married Heterosexual Men with Premature Ejaculation: A Pragmatic, Randomized Controlled Trial" is the bonafide work of Dr. Debanjan Mandal towards MD Psychiatry Degree Examination of Tamil Nadu, Dr. M.G.R Medical University to be conducted in May 2018.

This work has not been submitted to any university in part or full.

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CERTIFICATE

This is to certify that the dissertation titled "The efficacy and safety of Clomipramine Hydrochloride versus Dapoxetine Hydrochloride in Married Heterosexual Men with Premature Ejaculation: A Pragmatic, Randomized Controlled Trial" has been initiated with Dr. Debanjan Mandal being the principal investigator and Prof. Prathap Tharyan as the guide.

Dr. Prathap Tharyan retired from service on 1st August 2017 and Dr. Saumil Dholakia, Professor of Psychiatry, is the guide for this dissertation from 2nd August 2017 onwards.

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This work has not been submitted to any university in part or full.

Dr. Saumil Dholakia, MD

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DECLARATION

I hereby declare that this dissertation titled "The efficacy and safety of Clomipramine Hydrochloride versus Dapoxetine Hydrochloride in Married Heterosexual Men with Premature Ejaculation: A Pragmatic, Randomized Controlled Trial" is a bonafide work done by me under the guidance of Dr Saumil Dholakia, Professor of Psychiatry, Christian Medical College, Vellore.

This work has not been submitted to any university in part or full.

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IRB APPROVAL LETTER

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Ethics Committee Registration No: ECR/326/INST/TN/2013 issued under Rule 122D of the Drugs & Cosmetics Rules 1945, Govt. of India

May 22, 2017

Dr. Debanjan Mandal,
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Sub: **Fluid Research Grant: New Proposal:**
The efficacy and safety of Clomipramine Hydrochloride versus Dapoxetine Hydrochloride in Married Heterosexual Men with Premature Ejaculation: A Pragmatic, Randomized Controlled Trial.
Dr. Debanjan Mandal, Employment Number: 21116, PG Registrar, Department of Psychiatry, Unit II, Dr. Prathap Tharyan, Professor of Psychiatry, Dr. Saumil Dholakia, Associate Professor, Dr. Munaf Nandyal, Assistant Professor, Dr. Akhil Abhijnhan, Assistant Prof, Dr. Arnab Mukherjee, Senior Resident, Dr. Sanmitra Dasgupta, Assistant Professor Department of Psychiatry, Dr. Antony Devasia, Professor and Head, Dr. Partho Mukherjee, Assistant Professor Department of Urology...

Ref: IRB Min. No. 10649 [INTERVE] dated 19.04.2017

Dear Dr. Debanjan Mandal,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
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CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

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Ref: IRB Min. No. 10649 [INTERVE] dated 19.04.2017

Dear Dr. Debanjan Mandal,

The Institutional Review Board (**Silver**, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "The efficacy and safety of Clomipramine Hydrochloride versus Dapoxetine Hydrochloride in Married Heterosexual Men with Premature Ejaculation: A Pragmatic, Randomized Controlled Trial" on April 19th 2017.

The Committee reviewed the following documents:

1. 1. IRB Application format
2. Information sheet (English)
3. Informed Consent form (English and Tamil)
4. Data Collection Form
5. The Antidepressant Side-Effect Checklist (ASEC) (English and Tamil)
6. Premature Ejaculation Profile(English and Tamil). 2 of 5

7. Cvs of Debanjan Mandal, Antony Devasia , Arnab Mukherjee , Akhil Abhijnhan, Munaf Nandyal, Prathap Tharyan , Sanmitra Dasgupta, Saumil Dholakia,
8. No. of documents 1 – 7.

The following Institutional Review Board (Silver, Research & Ethics Committee) members were present at the meeting held on April 19th 2017 at 9.45 am in the BRTC Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Affiliation
Dr. L. Jeyaseelan	MSc, PhD, FSMS, FRSS	Professor, Biostatistics, Secretary (Research Committee), IRB, CMC, Vellore	Internal, Statistician
Dr. George Thomas	MBBS, D Ortho, PhD	Orthopaedic Surgeon, St. Isabella Hospital, Chennai, Chairperson, Ethics Committee, IRB, Chennai	External, Clinician
Dr. Jayaprakash Muliyil	BSc, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, Vellore	External, Scientist & Epidemiologist
Dr. Anuradha Bose	MBBS, DCH, MD,MRCP, FRCPCH	Professor, Community Medicine, CMC, Vellore	Internal, Clinician
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, Additional Vice Principal (Research), Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC, Vellore.	Internal, Clinician
Dr. Suceena Alexander	MBBS, MD, DM	Associate Professor, Nephrology, CMC, Vellore	Internal, Clinician
Prof. Keith Gomez	BSc, MA (S.W), M. Phil (Psychiatry Social Work)	Student counselor, Loyola College, Chennai, Deputy Chairperson, Ethics Committee, IRB	External, Lay Person & Social Scientist
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Dr. Jiji Elizabeth Mathews	MBBS, DGO, MD,	Professor, Obstetrics & Gynaecology, CMC, Vellore	Internal, Clinician
Dr. Vinitha Ravindran	PhD (Nursing)	Professor & Addl. Deputy Dean, College of Nursing, CMC, Vellore	Internal, Nurse

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "The efficacy and safety of Clomipramine Hydrochloride versus Dapoxetine Hydrochloride in Married Heterosexual Men with Premature Ejaculation: A Pragmatic, Randomized Controlled Trial" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

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The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Fluid Grant Allocation:

A sum of 43,629/- INR (Rupees Forty three thousand six hundred and twenty nine only) will be granted for 24 months

Yours sincerely

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

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PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled "The efficacy and safety of Clomipramine Hydrochloride versus Dapoxetine Hydrochloride in Married Heterosexual Men with Premature Ejaculation: A Pragmatic, Randomized Controlled Trial" of the candidate Dr. Debanjan Mandal with registration number 201628252 for the award of MD in the branch of XVIII Psychiatry.

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I am indebted to all the study participants, who willingly and patiently agreed to take part in the study.

I thank the research committee of Christian Medical College, Vellore for granting approval and funding of this project.

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I thank God Almighty for being with us, and for giving us the strength to go through with this project.

Abstract

Title of the abstract: The efficacy and safety of Clomipramine Hydrochloride versus Dapoxetine Hydrochloride in Married Heterosexual Men with Premature Ejaculation: A Pragmatic, Randomized Controlled Trial

Department: Psychiatry

Name of the candidate: Dr. Debanjan Mandal

Degree and subject: MD, Psychiatry

Name of the guide: Dr. Saumil Dholakia

Background:

Dapoxetine and Clomipramine are used in treating patients with premature ejaculation. Previous trials have demonstrated advantages for Dapoxetine compared to other SSRIs in increasing IELT (intravaginal ejaculatory latency time), and reducing distress due to premature ejaculation, but no head to head comparisons have been conducted against Clomipramine (tricyclic antidepressant) that has been shown to be effective in treatment of premature ejaculation.

Objective:

Objective of the study was to evaluate the efficacy and safety of six weeks of daily oral Clomipramine (25 to 50 mg) versus oral Dapoxetine on demand (30 mg; once a week for six weeks or for six doses) in the treatment of Premature Ejaculation in heterosexual, married men.

Methods:

Design: The study was designed as a pragmatic, randomized, parallel group, allocation-concealed, assessor-blinded, active-controlled trial

Setting: Urology, Andrology and Psychiatry department **o**utpatient services of a teaching general and multi-specialty referral hospital in south India

Participants: Eighteen married adults presenting with premature ejaculation as a result of a non-organic etiology and fulfilling selection criteria who provided written (and video-taped) informed consent for study participation. The target sample size is 120 and the study is ongoing.

Interventions: Oral Clomipramine (25 mg daily for 1st week and 25-50 mg for subsequent 5 weeks, depending on participants' preference) or oral Dapoxetine 30 mg on demand (taken 1-3 hours prior to intercourse) for 6 doses (recommended once weekly for 6 weeks). Additional non-pharmacological interventions were delivered to each participant by the means of a structured psycho-education module.

Main outcome measures: The primary outcome is the improvement of premature ejaculation at six weeks (or after the first six sexual encounters) which was measured by validated patient-reported measures (1) the Premature Ejaculation Profile (PEP) that measures changes in the participants subjective sense of control over ejaculation, distress related to PE, interpersonal difficulty and satisfaction with sexual intercourse, and (2) participant-reported Clinical Global Impression of Change (CGI-C). Secondary outcomes were adverse effects

of the interventions using the validated ASEC side effects rating scale, and drug discontinuation.

Results:

Eighteen patients have been recruited thus far in this ongoing study. Two of them have completed the study, both in the Clomipramine arm. One patient in the Dapoxetine arm has dropped out after third week of study, due to adverse drug reactions of insomnia and dry mouth. Analysis was done by intention to treat, where the last recorded outcome of participants who were lost to follow up was used to impute their final outcome. All three of the participants showed trajectory towards improvement in all four domains of PEP. One patient in Clomipramine arm reported a CGI score of 2 (“better”) at the end of six weeks. However, analytical data of outcome measure done on these three patients was not statistically significant. Patients in the Clomipramine group reported adverse reactions of constipation, drowsiness and increased body temperature.

Descriptive analysis of the baseline profile of patients recruited till now (N=18) showed that most of them were young, less than 10th standard educated married adults, presenting mostly alone, with very poor control over their ejaculation, poor satisfaction from sexual intercourse, extremely distressed in relation to early ejaculation and experiencing moderate difficulty in interpersonal functioning due to premature ejaculation and have multiple sexual misconceptions-the most prominent being the size of the penis and a significant proportion of them have masturbatory guilt.

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Index of Tables, Charts, Diagrams

Introduction

Sexual satisfaction as a construct has evolved over the last decade from being just a human experience of the last stage of the sexual response cycle to becoming a sexual right (1). Sexual satisfaction is defined as "an affective response arising from one's subjective evaluation of the positive and negative dimensions associated with one's sexual relationship" and it is often considered a key factor in individual's quality of life, physical and psychological health and overall well-being (2) .

The factors affecting sexual satisfaction are varied. Ecological theory proposes to understand contributory factors as a function of four interrelated levels: a) the microsystem (individual characteristics like age, gender, depression, child sexual abuse, personality, self-esteem etc.); b) the meso-system (immediate environment like sexual assertiveness, marital relationship etc.); c) the exo-system (social network and status like parenthood, family relationships etc.); and d) the macro-system (political ideology, religious beliefs etc) (2).

Sexual satisfaction found its way into medical research through the controversial Kinsey's reports (3) in the early 1950's which led to a change in public perception of human sexuality from a value-based experience and the emergence of "scientific sexology". Subsequent work by Masters and Johnson led to the description and publication of the human sexual response cycle in the mid-1960's and helped to successfully align sexology with medicine (4) . The early 1990's saw the use of better and more rigorous methodology to survey sexuality and

sexual satisfaction by Laumann and his colleagues (5) to better delineate what defines human sexual satisfaction.

Around the same time, the experience of an unexpected side effect of "marked penile erections" in volunteers undergoing trials of a drug called Sildenafil citrate to treat hypertension and angina created ripples in the medical world and officially announced the introduction of pharmaceutical industry into the world of research in sexual satisfaction (6) . What was till now an observational research domain was opened to the vast dimensions of pharmacological interventional research.

As further research into this field progressed, it became apparent that there were two common sexual disorders— Erectile dysfunction (ED) primarily affecting ageing men with comorbid diabetes mellitus or cardiovascular diseases and Premature Ejaculation (PE) which can affect men of all ages that is not typically associated with organic disorders and is associated with brain Serotonergic dysregulation (7).

The use of Phosphodiesterase inhibitors revolutionized the treatment for ED. However, it was not until 2014 that the European association of Urology guidelines endorsed on-demand Dapoxetine (a selective serotonin reuptake inhibitor) for the management of Premature Ejaculation and this is currently the only drug licenced specifically for the treatment of PE (8).

Clomipramine is a Tricyclic antidepressant which has been found to be useful in PE. Studies on the use of Clomipramine compared to other SSRI's showed daily

Clomipramine to be superior to other SSRI's in improving ejaculatory latency and satisfaction with ejaculatory control (8).

Concerns have been raised with use of on-demand Dapoxetine and surveys have revealed that people with PE preferred daily drug therapy over on demand therapy (9). Clomipramine used in the low doses required for the treatment of PE is an affordable option, and efficacy is reported in over 60% of participants. To date, there are no head to head Randomized Controlled Trials (RCTs) comparing the efficacy of Dapoxetine and Clomipramine.

This pragmatic, randomized, allocation-concealed, assessor-blinded controlled trial was conducted to evaluate the safety and efficacy of 6 weeks of daily oral Clomipramine (25-50mg) versus oral Dapoxetine (30mg once in a week for 6 weeks or for 6 dosages in the 6 weeks) in heterosexual married men with a DSM 5 diagnosis of Premature Ejaculation.

Efficacy was determined by the response of the participants to the Premature Ejaculation Profile, which includes domains of subjective sense of control over ejaculation, distress related to PE, interpersonal difficulty and satisfaction with sexual intercourse.

Objectives and Aims

The objective of this pragmatic, randomized, allocation-concealed, assessor-blinded controlled clinical trial was to evaluate the efficacy and safety of oral Clomipramine in flexible low doses (25 to 50 mg) given daily for six weeks versus Dapoxetine 30 mg taken on demand for six doses (preferably once a week, or for six doses over the six weeks of the trials) in adult, heterosexual, married, male, outpatients presenting with a DSM 5 diagnosis of Premature Ejaculation to the Urology, Andrology and Psychiatric Clinics of a teaching hospital in the domains of subjective sense of control over ejaculation, distress related to PE, interpersonal difficulty and satisfaction with sexual intercourse and clinical global improvement.

The specific Aims of the study were:

1) To assess the efficacy of Clomipramine given in daily flexible dosages of 25 to 50mg for 6 weeks duration versus Dapoxetine 30mg taken on demand basis for six weeks on once a week basis (or six doses, whichever is earlier) in patients with a DSM-5 diagnosis of Premature Ejaculation on validated patient reported outcome measures –Premature Ejaculation Profile (PEP) that assesses the participants' subjective sense of control over ejaculation, distress related to PE, interpersonal difficulty and satisfaction with sexual intercourse and participant reported Clinical Global impression of Change (CGI-C).

2) To assess the safety of the above two interventions with the help of validated Antidepressant Side effect checklist (ASEC) rating scale and rates of either drug discontinuation.

Review of Literature

This section selectively reviews the existing International and Indian literature regarding the history of Sexuality, the anatomy and physiology of ejaculation, the aetiological evaluation of the diagnosis of Premature Ejaculation, the background of assessment of Premature Ejaculation in research settings and the present evidence for the pharmacological treatment of Premature Ejaculation. The tools and the methods used in the studies that generated the present evidence for the pharmacological treatment of Premature Ejaculation are reviewed in order to provide information relevant to the methods used in this study and to clarify the results and interpretations of this study.

Historical and cultural dimensions to human sexuality:

Human fascination in the pursuit and quest for the perfect sexual experience has been described since ancient times. Until recently, the understanding of premature ejaculation (PE) was influenced by various cultural diversities. The importance of ejaculation in the art of love and sexuality has been depicted in many ancient cultures and times.

Sexuality has been depicted in various Hindu writings and other art-works through the ages. The Hindu god "Lord Shiva" is often represented with an erect phallus, symbolizing power and fertility (10). Semen has been considered as precious and powerful substance in Indian cultures and there exist many myths around it (11). Many of the ancient Indian religious books, e.g. the Atharva Veda, mentioned that 100 drops of blood are required to make one drop of semen. Loss

of semen has been considered as a loss of strength. The culture bound syndrome called ‘‘Dhat syndrome” has its roots in these beliefs (12).

The ‘Kama Sutra’ is an ancient Indian Hindu text widely considered to be the standard work on human sexual behaviour in Sanskrit literature. Mallanaga, a bachelor belonging to the Vatsyayana sect, wrote this famous book between the 1st and 4th centuries AD. It was also described as the lifestyle book of that era. The first part of the book described different ways to find and keep a partner, the importance of personal discipline, and various suggestions linked to sexuality, e.g. freshening of breath by chewing betel leaves, range of sexual positions etc (13). The second part of “Kama Sutra” discusses exclusively about various aspects of sexual intercourse. Different lengths of time to ejaculation were given different merits. It was proposed that the passion of the man is intense during the first time of sexual union, but it does not remain the same on subsequent sexual encounters. The author noticed that the female partner showed more love to the male partner when he was long-timed, but she would be dissatisfied with him if he was short-timed. He inferred that men engaged in coital act would be somehow satisfied after emission irrespective of time, but it was not the same with women. This is a very early reference in the literature to the fact that PE causes distress, bother and dissatisfaction to the sufferer and the partner, and also conflicts in the romantic relationship.

The English translation of ‘Kama Sutra’ was initially published in 1876 in Britain, but was considered to be far too lewd by Victorian England and thus banned subsequently. It was not officially available until 1963.

Themes based on human sexuality have been described in Christian writings also. The Bible, considered as the holy book for Christians, states that semen was intended to be deposited only in vaginas, the main purpose being that of procreation. Men were told-"Be fruitful, and multiply and replenish the earth" (Genesis 2). The punishment for not obeying God's Law was death, which was illustrated in Onan's story. Onan was forced by his father Judah, to marry his brother's widow Tamar. But Onan did not love her, and he knew that the offspring would not be his; and due to that he could not ejaculate into her vagina during coitus. He spilled it (his semen) outside. The Lord was displeased by this incident and therefore He slew him (Genesis 38) (14).

Description of sexuality in Chinese culture dates back to many ancient dynasties. Sex was positively encouraged as the means to good health during The Tang Dynasty (618–907 AD). This era was considered to be full of sexual freedom. Sex was seen as the very essence of nature and harmony. Frequent and long-lasting sex was considered as a mean of promoting balance between the 'Yang' (positive, bright, masculine) and the 'Yin' (negative, dark, feminine), by the early Taoist philosophers. Also there was beliefs that when a man ejaculates (''chi'') semen, he becomes weak for the next sexual act. Therefore methods to delay or suppress ejaculation were considered to be beneficial and they became very popular. Over the years, however, attitudes to sexuality became more restricted, repressed and regulated, e.g. in the Ming Dynasty (1368–1644), and the Quing Dynasty (1644–1911) (15).

Erotic life flourished at all levels of ancient Egyptian society (16). The famous temple carvings, sculptures and paintings describe various themes on 'Life', the 'after-life', 'Fertility', and 'Creation'. There were lots of interesting remedies for sexual problems in ancient Egypt. An important icon was the lotus flower, which was thought to carry magical powers (17). It arose at the beginning of 'time' from the waters of Nun ('the original waters'). The lotus flower was believed to open up at the first ray of the Sun and release a hyacinth-like aroma. This scent when smelled over some time might have considerable effect on alteration in consciousness (18). This may have had the effect of reducing anxiety, and thus possibly delaying ejaculation. However, there was no specific mention of PE.

Among other famous writings on sexuality, a book named 'The Perfumed Garden' is worth mentioning. It was written by Sheikh Nefzawi (around 1500 AD), who was an adviser to the 'Grand Vizier of Tunis' (emperor of Tunisia).This book is considered by many as the Islamic version of the 'Kama Sutra' (19). Specific reference to PE was made in the book, but treatment options were not mentioned.

Over the years many more efforts have been made to elaborate human sexual behaviour. Recent epidemiological, clinical and neurobiological research has provided new insights into the complex mechanisms of human sexuality. Specifically for premature ejaculation, understanding has improved in the domains of neuroanatomy and neurobiology of ejaculation, and various other dimensions like epidemiology, psychosocial and relational effects, and pathophysiology of PE (20–26). In parallel with this new understanding, the

standard classification, definition, evaluation, diagnostic criteria, and treatment options for PE has undergone a paradigm change (27–31).

Anatomy and Physiology of Ejaculation:

The renowned American sexologists Masters and Johnson have been credited with the first major attempt to elaborate human sexual behaviour in an observation based descriptive method (32). It can be considered as the first scientific way to explain human sexual behaviour and response. They postulated that the normal human sexual response cycle is psycho- physiological in nature, and divided it into four interactive phases: excitement, plateau, orgasm and resolution. All these phases were described in both males and females. However, the sense of sexual pleasure is heterogeneous, and is influenced by many other interactive and complex factors, e.g. individual (anatomical and physiological), developmental, situational (life stage), psychological, interpersonal, social and cultural factors.

The first phase, the phase of excitement occupies the most of the time of the cycle. It can last from several minutes to several hours. Heightened excitement before orgasm is seen for 30 seconds to three minutes. Some characteristic genital and extra-genital changes have been described in this phase. The extra-genital changes consist of skin flush, maculopapular rash appearing on abdomen and spreading to anterior chest wall, face, neck, shoulders and forearms, contraction of facial, intercostal muscles voluntary group of muscles like Rectus Abdominis

etc. The genital changes in males include rapid erection (in 10 – 30 seconds) of penis caused by vaso-congestion of erectile bodies of corpus cavernosa of shaft; tightening and lifting of scrotal sac and elevation of testes. With heightened excitement, further increase in size of glands, diameter of penile shaft, size of testes over unstimulated state is seen. Genital changes seen in females consist of congestion of the clitoris, labia majora and minora and opening up of the introitus. Other changes seen in this phase are - in breasts: inconsistent nipple erection with heightened excitement before orgasm; tachycardia (up to 175 beats per minute); rise in systolic blood pressure by 20 -80 mm and in diastolic blood pressure by 10 - 40 mm; increased respiratory rate etc. In this phase loss of erection may occur with introduction of asexual stimulus, loud noise etc. In an inexperienced male, this phase may last as short as 45-60 seconds.

The plateau phase which follows is characterized by slight exaggeration of the changes in the excitement phase with increase in heart rate, blood pressure and respiratory rate and increase in size of the testis in males and rise of the uterus out of the true pelvis in females.

The orgasmic phase is the shortest of the four phases, lasting about three to 15 seconds. It consists of intense physical activity characterized by expulsive contractions along the length of the penile urethra causing ejaculation of the seminal fluid which varies both in volume and content from one individual to the other and in the same individual from time to time. Ejaculation of semen happens in the final stage of coitus in mammalian males. It is followed by a refractory period during which erection reduces and sexual responses are inhibited.

Ejaculatory process consists of the synchronized succession of few physiological events, and it can be divided in to two distinct phases, namely emission and expulsion. Emission refers to the secretion of the different components of the seminal fluid from accessory sex glands and testes. The seminal secretions flow into the posterior urethra via phasic contractions of the glands and their respective ducts. At this time, the bladder neck is firmly closed to prevent backflow into the bladder. This is followed by expulsion of semen, which is mediated by an intense burst of contractions of pelvic and perineal striated muscles. These two processes are intimately linked. However, they have been studied distinctively using specific physiological markers. They also can occur independently from each other in certain pathophysiological conditions and experimental situations (33).

The last phase of resolution involves return to normal size and vasculature of the genitalia. This usual takes minutes but is dependent on the degree of orgasmic reaction (34). Later Kaplan (35) and Levin (36) postulated another model to explain human sexual behaviour. This model consists of the following phases: desire, excitation, orgasm, and resolution. It closely follows the previous model, but differs in certain aspects, e.g. much importance has been given on the desire phase which precedes excitation phase, thus highlighting importance of psychological factors in human sexual behaviour. This model has been widely accepted by the medical fraternity. Overall, the different aspects of male sexual function include sexual desire, erection, ejaculation, and orgasm. Each of these is controlled by a complex and coordinated interplay of multiple components of the brain, spinal cord, and relevant peripheral organs.

Historical evolution of the diagnostic construct of premature ejaculation:

Importance of the duration of the coital act has been mentioned in many writings in various ancient cultures. The phenomenon of PE is well known for ages. But the notion to consider it as a disorder arose only in the past two centuries. Ancient Greek writings mentioned terms like "ejaculatio ante portas" (37), (literal meaning "ejaculation before the gate"), which actually meant "ejaculation before insertion of the penis into the vagina". Despite being well known as an entity, PE appeared for the first time in medical writings only in the nineteenth century (38). In 1887, Gross described the first clinical case of rapid ejaculation in the medical literature (39). In 1901, German psychiatrist Krafft-Ebing reported another similar case. He highlighted the phenomenon of an abnormally fast ejaculation, but did not use the term "praecox" or "premature" (40).

The understanding of PE evolved further in the twentieth century. There have been many hypotheses and theories on the mechanism and treatment options of PE, proposed by several researchers from various fields like psychology, sexual medicine, neurobiology, etc. These can be broadly classified into –

1. Somatic (urological or physiological),

2. Psychological (psychoanalytic or behaviouristic), and

3. Neurobiological-genetic approaches.

This is described in the following table (Table 1) –

Table 1 - Chronological evolution of concept of PE

Year	Authors	Postulated etiology and pathogenesis of PE	Advocated treatment of PE
1917	Karl Abraham	Considered PE as a neurosis, linked it to unconscious conflicts	Psychoanalysis, and psychoanalytic psychotherapy
1943	Bernhard Schapiro	Postulated PE as a psychosomatic disorder, proposed link with a weak genital system. Classified PE into 2 subtypes - Type A and B	Topical anaesthetic Creams
1970	William Masters, Virginia Johnson	Explained PE as a behavioural disorder, linked to self-learned behaviour	Behavioural treatment, e.g. squeeze technique
1998	Marcel Waldinger	Postulated Lifelong PE as a neurobiological-genetic disorder, emphasized correlation with central serotonin neurotransmission dysfunctions. Classified PE into 4 subtypes – Lifelong, Acquired, natural variant, PE like ejaculatory dysfunction	Medication acting on serotoninergic pathways, e.g. Selective serotonin reuptake inhibitors (SSRIs), Clomipramine etc.

Chronologically the evolution of understanding of PE can be divided into –

1. The First Period (1917–1950):

Neurosis and Psychosomatic Disorder –

The first few decades of the twentieth century saw the rise of psychoanalytic theories of mind. One of the pioneers of these theories was Karl Abraham. He described the phenomenon of rapid ejaculation in 1917, and termed it "ejaculation praecox" (41). In psychoanalytic school, PE was considered as a neurosis related to unconscious conflicts (41) (42). Classical psychoanalysis was the proposed treatment of choice.

The other school in those years used a somatic approach. It consisted primarily of urological views to explain PE. The possible mechanisms proposed were –

1. Hyperesthesia of the glans penis,

2. Short frenulum of the foreskin, and

3. Changes in the posterior section of the urethra, particularly at the verumontanum

Advocated treatment options consisted of –

1. Anaesthetizing ointment for local application,

2. Solutions of silver nitrate for local application,

3. Incision of the frenulum, and even

4. Total destruction of the verumontanum by electrocautery. etc

In 1943, the pure psychological view of Karl Abraham was challenged by the German endocrinologist Bernhard Schapiro. He argued that PE is a "psycho-somatic" disturbance arising from a complex combination of a psychologically overanxious constitution and 'an inferior ejaculatory apparatus as a point of least resistance for emotional pressure' (43).

Schapiro described two types of premature ejaculation –

1. Type A (the sexually "hypotonic" type) –mainly having problems with poor erection of penis. They were believed to respond well to nerve tonics, testosterone, sports, prolonged sexual rest, hydrotherapy, and electrotherapy. In the later years these patients were distinguished as having 'secondary' or 'acquired' type of PE.

2. Type B (the sexually "hypertonic" or "hyper-erotic" type) – having a persistent tendency to ejaculate rapidly from the first act of sexual intercourse. They were mainly treated with sedatives. In the later years these patients were distinguished as having 'primary' or 'lifetime' type of PE.

Schapiro did not suggest genetic factors behind PE. However, he noted multiple men from same family suffering from PE (43) (44).

In addition to the above mentioned treatments, Camphora monobormata, belladonna, strypticine, and papaverine were used for treatment of PE in this era.

2. The Second Period (1950–1990):

Learned Behaviour –

American sexologists William Masters and Virginia Johnson came to prominence in 1950s. They rejected the psychoanalytic and psychosomatic view of Abraham and Schapiro. They hypothesized that PE results from learned behaviour (33) (45). They argued that when a man experiences early or rapid ejaculation during initial intercourse(s), it results in habituation and performance anxiety, leading to persistent premature ejaculation later in life. This view was supported by findings from physiological experiments on human sexuality done by them, where they found importance of anxiety in dysfunctional sexual behaviour. Behaviour therapy was considered the mainstay of treatment for PE and other sexual dysfunctions, and was predominantly present in the medical literature.

However, the use of psychoactive drugs such as Clomipramine in the treatment of PE started gathering popularity in the 1980s.

3. The Third Period (1990–2005):

Neurobiology and Psychopharmacology –

Last three decade saw rise of neurobiological views. In 1996, Waldinger et al. proposed that lifelong PE has a neurobiological and genetically determined patho-physiological basis (31) (46). Role of diminished central serotonergic neurotransmission in ejaculation of semen was emphasized, and activation or

inhibition of specific 5-HT receptors was highlighted. This was supported by the outcome data of multiple animal studies, and also psychopharmacological treatment studies on PE (46). The previously held pure psychological and behaviouristic views of the etiology and pathogenesis of lifelong PE were thus rejected by Waldinger.

The introduction of the selective serotonin reuptake inhibitors (SSRIs) in the early 1990s, brought a major change in the treatment of PE (47). SSRIs were shown to be efficacious in delaying ejaculation. Their side effect profile was more favourable compared to other previously used medications. These factors contributed to a new trend of SSRIs becoming one the main pharmacological agents for treatment of PE, although it was off-label use. They were being used both as daily as well as an on-demand basis.

Another important event was the introduction of the concept of Intravaginal Ejaculatory Latency time (IELT), by Waldinger et al in1994, and the subsequent use of the stopwatch technique by the partner to measure the same. IELT was defined as the time between intravaginal entry and the beginning of intravaginal ejaculation.

During the initial years of 1990s, most of the sexologists found it difficult to accept the new neurobiological explanatory model of lifelong PE, and also the effective treatment by SSRIs. This view gradually gained popularity over the next 10 years, owing to writings by sexual health specialists who originally believed in other school of thoughts. Worth mentioning among them is Pierre Assalian, a

Canadian psychiatrist, who wrote an article suggesting peripheral nervous system involvement in mechanism of PE, thereby suspecting whether PE was really always psychogenic (48).

4. The Fourth Period (2005–Present):

Era of Genetics and Pharmaceutical Industries–

Newer developments in genetic research have been promising in finding etiological correlates of PE. Genetic polymorphism studies, DNA researches (49) (50) in men with lifelong PE have started to indicate that some polymorphisms of the central serotonergic and dopaminergic system are associated with the duration of ejaculation (IELT) (51) (52). During this period, for the very first time in history a drug was officially approved by the NICE guidelines and European Medicines Agency (EMEA) for the treatment of PE, the drug being Dapoxetine, a short acting SSRI (53). Subsequently several pharmaceutical companies have started showing interest in drug treatment of PE.

In contrast to the opinion- or authority-based approach of the last century, both the third and fourth period (1990–present) are characterized by emphasis on evidence-based animal and human research, which mainly pertains to psychopharmacological, genetic, neurophysiological, and clinical research (54).

Epidemiology of Premature Ejaculation –

Compared to the past, there has been recent increased interest in research in premature ejaculation (PE). Therefore the need for better understanding of the epidemiological factors has been emphasized in medical literature. However, there is lack of epidemiological studies on sexual dysfunction overall, specifically for PE, especially in India (55) (56).There are many contributing factors to it. Firstly, measuring the burden of sexual problems is a challenging task. There has been lack of universally accepted definitions and criteria for diagnosis of PE. There was also lack of methodologically sound observational studies, which lead to difficulty in measuring the true magnitude of this sexual disorder (5). Moreover, men with PE often are found to be reluctant to report this problem, mainly due to their concerns of socio-cultural factors, e.g. stigmatization. This is seen more in face-to-face interviews compared to telephone interviews. These obstacles reflecting the sensitive nature of this condition may result in systematic biases (5). On the other hand, sometimes apparently healthy individuals self-report PE, with the belief that they might get benefitted from participating in research studies. Therefore, caution is needed while evaluating the presented data due to the aforementioned limitations in epidemiologic studies on PE.

Initial studies on prevalence of sexual dysfunctions were suggestive of high prevalence rates of PE in the general population (57). Dunn was credited with one of the first large-scale, systematic epidemiological study on sexual dysfunctions in the general population carried out in England, in 1998.In this study, 31% of the patients reported that the complaint of “having difficulty with ejaculating

prematurely" had happened at some point in their lives, and 14% complained about it in the past three months (58).

In 1999 the National Health and Social Life Survey (NHSLS) done in the USA, revealed that 31% of the 1410 participants complained of "climaxing or ejaculating too rapidly during the past 12 months" (59). The clinical variables associated with this complaint were found to be factors such as having sex with a new and sexually attractive partner or abstaining from sex for a longer period of time (60).

Findings from these large scale epidemiological studies contributed significantly towards the widely held notion that Premature Ejaculation is the "most common sexual dysfunction" in men, despite of the limitations of the studies.

In 2005, the Global Study of Sexual Attitudes and Behaviours (GSSAB) was conducted in 29 countries, which remains the largest multinational survey performed in the field of sexual medicine till date. They followed DSM-IV-TR criteria to define PE, and used personal and telephone interviews and self-completed mailed questionnaires to interview 13,618 men between 40 and 80 years of age (61–65) This study revealed the worldwide prevalence of PE to be 23.75%, which is quite high (66).

Another major international study, namely the Premature Ejaculation Prevalence and Attitudes (PEPA) survey, using operational criteria (control and distress) of DSM-IV definition of PE found a high prevalence rate of 22.7 % prevalence rate in a sample of 12,133 international volunteers (24).

Major epidemiological studies are summarized in the following table (Table 2)–

Year	Author	Data collection methods	Method of sample Recruitment	Specific operational criteria	Sample size (n)	Prevalence rate (%)
1998	Dunn et al (58)	Mail	General practice registers—random stratification	Having difficulty with ejaculating prematurely	617	14 (past 3 months)
					618	31 (lifetime)
1999	Laumann et.al (NHSLS) (5)	Personal interview	National Representative (18–59 years)	Ejaculating too rapidly during past 12 months	1410	31
2002	Fugl-Meyer et al (67)	Interview	Population register (18–74 years)	Often ejaculating shortly after intromission during past 12 months	1475	9
2004	Rowland et al. (68)	Mailed questionnaire	Internet panel	DSM IV	16.3	1158

2004	Nolazco et al. (69)	Interview	Invitation to outpatient clinic	Ejaculating fast or prematurely	2456	28.3
2005	Laumann et al. (GSSAB) (66)	Telephone-personal interview/ Mailed questionnaires	Random (systematic) Sampling	Reaching climax too quickly during the past 12 months	13,618	23.75 (4.26 frequently)
2005	BasileFasolo et al. (70)	Interview (Clinician-based)	Invitation to outpatient clinic	DSM IV	12,558	21.2
2005	Stulhofer et al. (71)	Interview	Stratified sampling	Often ejaculating inless than 2 min	601	9.5
2007	Porst et al (PEPA) (24)	Web-based survey	Pre-existing internet panels	Control over ejaculation Distress	12,133	22.7

2009	Brock et al. (72)	Web-based survey + telephone interview	Internet panel (random sampling)	DSM III, Control , Distress	3816	16, 26, 27
2010	Traeen et al. (73)	Mailed questionnaire	Population register (random sampling)	Having PE frequently during the past 1 yr	11,746	26
2010	Amidu et al. (74)	Questionnaire	Random sampling	N/A	255	64.7
2010	Liang et al. (75)	Questionnaire	Random sampling	ISSM definition	7372	15.3
2010	Park et al. (76)	Mailed questionnaire	Stratified sampling	Suffering from PE	2037	27.5
2011	Serefoglu et al. (77)	Interview	Stratified sampling	Complains ejaculating prematurely	2593	20

2011	Christensen et al. (78)	Interview and Questionnaire	Population register (random sampling)	Having PE frequently in last year , and perceiving it as a problem (DSM IV)	5552	7
2011	Tang et al (79)	Interview	Primary care setting	PEDT ≥9	207	40.6
2012	Mialon et al. (80)	Mailed questionnaire	Convenience sampling (18–25 yrs)	Control over ejaculation; Distress	2,507	11.4
2012	Shaeer et al (81)	Web-based survey	Online advertisement	Ejaculate before the person wishes, at least Sometimes	804	83.7

2012	McMahon et al. (82)	Computer assisted interview, online, or in person	N/A	PEDT ≥11	4,997	16
2013	Zhang et al. (83)	Interview	Random stratified sample	Self-reported PE	728	4.7
2013	Gao et al. (84)	Interview	Random stratified sample	Self-reported PE	3,016	25.8
2014	Akre et al. (85)	Mailed questionnaire	N/A	Control over ejaculation, Distress	3,695	10.9

Table 2 - Major epidemiological studies on PE

Indian studies –

One of the first observational studies in male sexual dysfunctions in India was done by Bagadia et al. in 1959, where he found correlation with many psychosomatic and socio-cultural factors. Another epidemiological study done by him on 258 men with sexual problems as main concerns revealed the following prevalence rates: anxiety over nocturnal emission (65%), passing semen in urine (47%) as main problems in the unmarried group; premature ejaculation (34%), impotence (48%),and passing semen in urine(47%) in married group (86).

Nakra et al in a study done in 1977(87) found prevalence of PE as 25.3% in a sample of 150 men with sexual problems attending psychiatric unit of a teaching general hospital. They also concluded that PE is a state of hyper-sexual arousal. Past masturbatory habit and associated guilt, nocturnal emission and associated misconception that loss of semen is harmful to health were commonly seen in men with PE and other sexual dysfunctions (88).

A study done by Kar and Varma in 1978 comparing 72 married psychiatric patients and 80 married controls did not find any major difference between prevalence of PE; 48% in ‘patient group’ and 40% in ‘control group’ (89).

PE, Erectile dysfunction (ED), and combination of ED and PE were reported by 12%, 30%, and 45% of subjects respectively in a study on 66 male patients, done by Avasthi et al in 1994 (90). Dhat syndrome, along with ED or PE, was reported by 9% of the subjects.

Verma et al in 1998 studied 1000 consecutive male patients with sexual disorders attending the psychosexual clinic, and found PE (77.6%), nocturnal emission (71.3%), masturbatory guilt (33.4%), small size of penis (30%), ED (23.6%), and excessive worries about nocturnal emission (19.5%) as common complaints (91).

A study done by Gupta et al in 2004, on 150 patients attending dermatology OPD for psychosexual problems revealed the following prevalence rates: PE - 16.6%, ED - 34%, Dhat syndrome -15.3%, nocturnal emission -14% (92).

Kendurkar et al (2008) reviewed the medical records of 1242 patients attending a marriage and sex clinic from 1979 to 2005, and found PE being the most common complaint and the most commonly diagnosed clinical entity, followed by ED and Dhat syndrome (93).

TSS Rao et al conducted an epidemiological study of sexual disorders in south Indian rural population, and found prevalence of PE to be 8.76% in a sample of 742 men. ED was found in 15.77%, male hypoactive sexual desire disorder (HSDD) in 2.56%; and 21.15% were diagnosed to have one (or more) sexual disorder (55).

It can be inferred from the above mentioned study findings that prevalence of PE in clinical settings and general population is high, and it is one of the commonest male sexual dysfunction in India and all over the world. However, there are limitations of these studies and lack of epidemiologic studies with scientifically sound sampling methods.

Premature ejaculation – definitions, concepts, classification:

There has been long standing debate about how to define the diagnostic parameters of this condition. The definitions and diagnostic systems for PE have evolved over a period in time.

The International Statistical Classification of Diseases and Related Health Problems (ICD - 10), by the World Health Organization (WHO), defines Premature Ejaculation (PE) as a sexual disorder characterized by persistent or recurrent ejaculation before or after penetration and before the person wishes it and the inability to control ejaculation sufficiently for both partners to enjoy sexual intercourse (94). ICD mentions that in severe cases ejaculation may occur even before vaginal entry or in the absence of an erection.

The definition of PE underwent a change with the introduction of concept of Intravaginal Ejaculatory Latency time (IELT) introduced by Waldinger et al and the subsequent use of stopwatch technique by the partner to measure the same (95) (96). IELT was defined as the time between intravaginal entry and the beginning of intravaginal ejaculation.

DSM 5 (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; by American Psychiatric Association) mentions the following criteria for defining PE –

1. Consistent ejaculation within 1 minute or less of vaginal penetration
2. Which has been experienced at least 75-100% of the time

3. Present over at least 6 months, and
4. Has caused clinically significant distress, sexual frustration and dissatisfaction between the partners.

DSM 5 covered 4 criterions and 7 sub features of Premature Ejaculation with slight change in nomenclature to Early Ejaculation to make the diagnosis less judgmental. It also provides a grade of severity based on the time duration with ejaculation occurring 30-60 seconds after penetration termed as mild, moderate being 15-30 seconds after penetration and severe being when ejaculation occurs prior to penetration, upon penetration or less than 15 seconds after penetration (95) (97).

The international society of sexual medicine has proposed the following constructs to define PE; ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy (98–100).

Initially, PE was classified as lifelong or acquired (101) (102). Acquired PE is secondary to other conditions and has been associated with chronic prostatitis, diabetes mellitus and hyperthyroidism. In these instances, PE is usually reversed when the underlying disorder is treated (103).

Subsequent to the inclusion of IELT, PE was classified into the following 4 syndromes (101) (99):

a) Lifelong PE (LPE)- starts from the first sexual encounter, occurs with every sexual partner, remains rapid throughout lifetime pointing towards a neurobiological cause with IELT is short (less than 2 minutes).

b) Acquired PE- Normal ejaculation experienced previously and may result from psychological/relationship/endocrine problems.

c) Natural Variable PE- inconsistent and irregular Early Ejaculations, The person has a perception of reduced control over Ejaculation and Psychotherapy is considered the first line of treatment.

d) Premature like Ejaculatory Dysfunction- IELT is normal or longer and PE is a subjective perception and the preoccupation is not accounted by any other psychiatric disorder.

Etiological and pathophysiological factors –

The exact etiology of PE is unknown. It is multifactorial and includes neurobiological and psychological components (101).

Neurobiological theories include central neurotransmitter levels and receptor sensitivity, evolutionary theories, degree of arousal, penile hypersensitivity the level of sex hormones, the speed of the ejaculatory reflex etc. (102).

Psychological explanations consist of the effects of anxiety, early experience and sexual conditioning, various sexual techniques, frequency of sexual intercourse and psychodynamic theories etc.

It has been proposed that etio-pathological factors of lifelong and acquired PE differ in certain aspects.

Lifelong PE (LPE) –

Neurobiological and genetic factors:

Abnormal Serotonergic activities have been postulated as a major etiological factor. Diminished central 5-HT neurotransmission, hyper-function of 5-HT1A receptors, hypo-function of 5-HT2C receptors have been shown to contribute to IELT of less than 1 minute (46) . This is supported by in vivo animal researches in 1980s (104) (105) (106) . However, this hypothesis is difficult to explore further due to absence of selective 5-HT1A and 5-HT2C receptor ligands for safe human usage (107) .

Some studies have shown development of LPE in first degree relatives of some male patients, highlighting the role of genetic factors, but it is not a classical Mendelian inheritable disorder affecting all male members of a family (43) (108) (29) .

Genetic polymorphisms and LPE:

Role of 5-HTTLPR polymorphism on duration of IELT in men with LPE was demonstrated in a study where difference between LL, SL, SS genotypes was noted. However, there were no significant differences when compared to a control group in reference to 5-HTT polymorphism alleles and genotypes (49) . Similar studies have shown influence of the C(1019)G polymorphism of the 5-HT1A receptor gene with comparison between CC, CG and GG genotypes (109), and Cys23Ser polymorphism of 5-HT2c receptor gene comparing wildtypes (CysCys) versus mutants (Ser/Ser) (110).

Acquired PE –

The risk factors and associated conditions are listed (Table 3) –

Risk factors	Conditions / Diseases
Psychological	Performance anxiety (111), interpersonal / marital problems (112), early difficult sexual experience, anxious personality traits
Urological	Chronic Prostatitis (75) (113), Varicocele (114)
Endocrine	Hyperthyroidism, Hypothyroidism (115)
Sexual symptoms	Comorbid Erectile Dysfunction (ED) (66), hypoactive sexual desire (116), female (partner) sexual dysfunction (117)

Of all the factors, role of "Anxiety" as an important etio-pathological factor of PE has been studied extensively and supported by multiple authors (44) (118) (119). The hypotheses include activation of the sympathetic nervous system resulting in reduction of the ejaculatory threshold, distraction from monitoring the level of arousal causing difficulty in recognition of the prodromal sensations that precede inevitable ejaculation (120) (121) (122).

In majority of cases, PE is found to be multifactorial.

The psychopathology of PE in the sexual response cycle is depicted in the following figure -

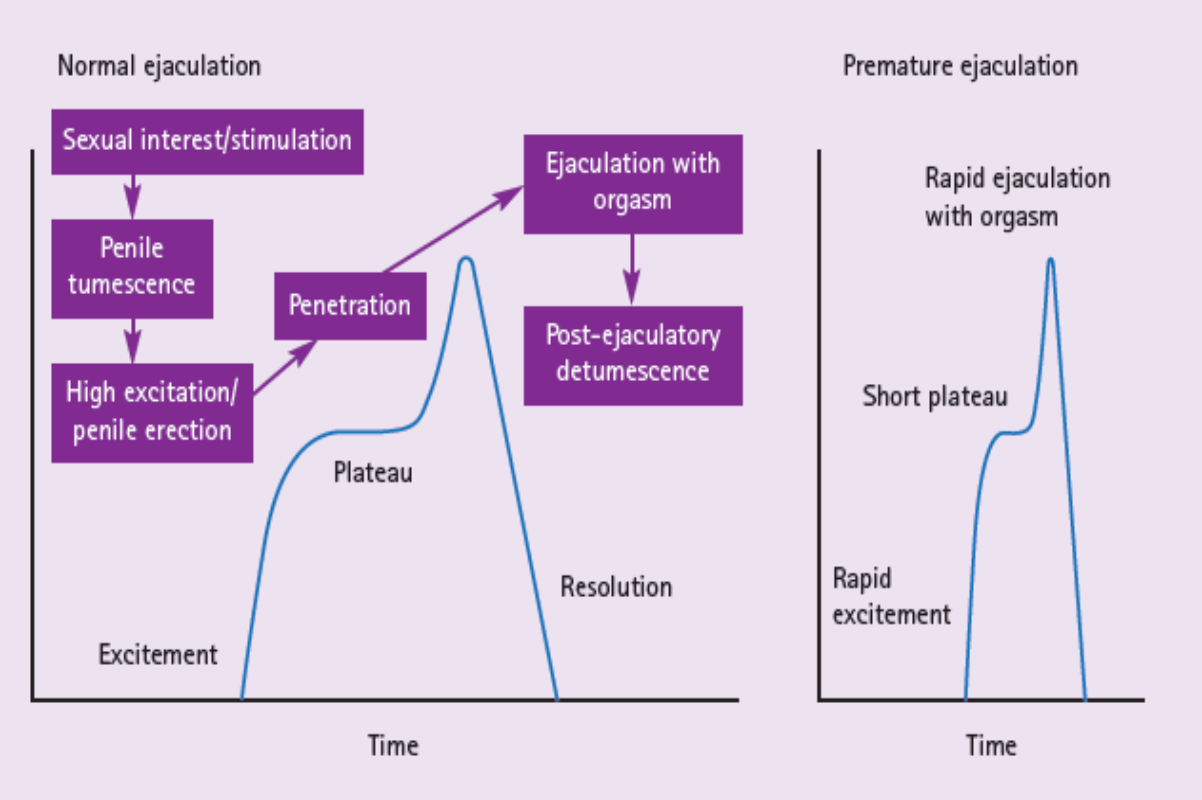


Figure 1 – Pathophysiology of PE in sexual cycle (123) (124)

Issues with respect to use of IELT in the assessment of PE:

Most definitions as discussed above use IELT as a threshold to measure, diagnose and hence treat PE. However, the relationship between the intravaginal entry and intravaginal ejaculation, ejaculatory control and sexual satisfaction is up for debate and the European guidelines do not recommend the use of IELT as an outcome measure in clinical practice (125). The fact that the partner measures the IELT during sexual intercourse with a stop watch is criticized by various clinicians as mechanical and far from clinical reality where sexual satisfaction and need for ejaculatory control are considered more important dimensions. The patient reported outcome assessments are criticized for being imprecise and subjective rather than objective though some studies have reported excellent correlation between stop watch measures of IELT and subjective reports (126).

There is currently no clear consensus on what constitutes a clinically significant threshold response to interventions for PE.

Major Assessment tools for PE and Sexual Satisfaction:

Table 4 - Major Assessment tools for PE and Sexual Satisfaction

Name	**Domain**	**Reliability Studies**	**Validity studies**	**Advantage**	**Limitation**
Premature Ejaculation	Perceived control;	USA Observational	Yes	Brief; easy to administer;	Lack of validated

Profile (PEP) (127)	satisfaction; personal distress; relationship problems	study- 0.66-0.74 (23) European studies-0.66-0.83 (25)		assesses outcomes; evaluates subjective and clinically important components	cut-off scores; only one question per domain
Index of Premature Ejaculation (IPE) (128)	Control; sexual satisfaction; distress	Good	Yes	Brief; easy to administer; assesses outcomes; evaluates subjective and clinically important components	Lacks norms and diagnostic cut-offs; not based on DSM 5 criteria
Premature Ejaculation Diagnostic Tool (129)	None	0.8	Yes	Screening questionnaire with cut-off scores.	Not based on DSM-5 domain
Golombok-Rust	12 domains	0.87	0.37	2 separate scales for	Not specific for PE.

Inventory of sexual satisfaction (GRISS) (130)				males and females. Can be used in couples	
Checklist for early ejaculation symptoms (CHEES) (126)	5-item diagnostic tool	Good	0.51-0.79	More in line with DSM-5 criteria	Gives a high, medium and low probability of PE according to cut off scores. May not be a good instrument to monitor treatment.

How is PE treated? Evidence from Non-pharmacological and Pharmacological interventions-

The treatment modalities for PE consist of pharmacotherapy and non-pharmacological interventions.

Non-pharmacological modalities -

Current psychotherapeutic approaches for PE aim at integration of psychodynamic, systems, behavioural and cognitive approaches within a short-term psychotherapy model. The principles of treatment are to learn to control ejaculation and manage and resolve the chronic negative effect that PE has on the man, partner and couple. The strategies include behavioural techniques like 'start-stop' or 'squeeze' method to delay ejaculation and cognitive techniques to address factors like performance anxiety, reducing spectatoring and improving diminished self-esteem (131).

The European guidelines state that in men for whom premature ejaculation causes few if any problems treatment should be limited to psychosexual counselling and education (132).

Before beginning treatment the guidelines recommend that it is essential to discuss expectations of treatment thoroughly. Various behavioural techniques have demonstrated benefit in treating premature ejaculation and are indicated for men uncomfortable with pharmacological therapy.

In lifelong premature ejaculation, the European guidelines state that pharmacological treatment should be the first-line option; behavioural techniques are not recommended as first-line treatment because they are time-intensive; require the support of a partner, and can be difficult to do (133).

Pharmacological therapies -

Pharmacotherapeutic measures for PE gained popularity over last 2 decades. The introduction of Selective Serotonin Reuptake Inhibitors (SSRIs) and Clomipramine has added new dimension to treatment of PE. Although the methodology of the initial drug treatment studies was rather poor, later double blind and placebo-controlled studies replicated the effect of Clomipramine and SSRIs to delay ejaculation (134). SSRIs studied for treatment of PE include Paroxetine (135) (136), Fluoxetine (8), Sertraline (8) etc. Other drugs which have been studied for treatment of PE include Tramadol, Sildenafil, and local anaesthetic gel (137) (138).

Clomipramine:

Clomipramine is a tricyclic antidepressant which has been shown to be useful in treatment of PE. Daily treatment with Clomipramine 25-50 mg has shown 4 to 6 fold-increase of ejaculatory latency time (8) (139), whereas on demand treatment has shown around 3 to 4 fold-increase of the same (135). Control over ejaculation has been shown to improve by 30% to 300%, and sexual satisfaction improved in around 52% patients after treatment with Clomipramine (8) (140) (141).

Common side effects of Clomipramine are dry mouth, drowsiness, giddiness and constipation which tend to settle with time.

Dapoxetine:

It is a newly developed SSRI which has been studied a lot in the field of treatment of PE. Most of the SSRIs take 2 weeks or longer to reach steady-state concentration, whereas Dapoxetine takes a short time to maximum serum concentration (about 1 hour) and rapid elimination (initial half-life of 1 to 2 hours). These attributes make Dapoxetine suitable for on-demand therapy for PE. Studies have shown that on-demand therapy with Dapoxetine 30-60 mg has shown to improve control over ejaculation by 250% to 300%, and 1.2 to 3.7 fold-increase of ejaculatory latency time (53) (142) (143) (144). Common side effects of Dapoxetine are nausea, yawning, and giddiness, which is not long lasting. On demand Dapoxetine was recently approved as drug of choice for Premature Ejaculation by NICE guidelines (133).

What do Men with PE prefer?-Evidence from trials:

A study done by Waldinger showed 88 previously never treated men who decided for themselves to be treated for PE regarding their preference for treatment. 81% of them preferred a drug for daily use, 16% preferred drug on demand while only 3 out of the 88 preferred a topical cream on demand. Their choice remained overall the same with 9 out of the 17 men who preferred on demand changing their preference to daily use drug after knowing the standard efficacy and safety

information of the drugs. The commonest reason given by them to prefer daily use was that daily use would have the least effect on the spontaneity of having sex (9).

The other advantages of daily drug use were noted to be tolerance to side effects after 2-3 weeks of treatment and prevent the mechanical, mandatory 1-6hr wait when taking on demand medication to delay ejaculation (145).

A systematic review and meta-analysis in 2015 (146) identified a total of 102 RCT's, most of them of unclear methodological quality, that used a variety of treatment strategies in PE. Twelve RCT's in this review on behavioural therapies showed them to be better than waitlisted control in improving IELT, sexual satisfaction, sexual anxiety and ejaculatory control. The evidence from these studies also showed that combined pharmacotherapy and behavioural strategies were better than either therapy alone.

Nine RCT's in the review on the use of topical anaesthetics found them to be significantly more effective than placebo, however, side effects of local irritation to both partners and loss of erection after more than 20 minutes were major drawbacks.

Among the SSRI's other than Dapoxetine, 42 RCT's in this review of mostly daily treatment for a period of 4 to 12 weeks showed Citalopram, Escitalopram, Fluoxetine, sertraline and paroxetine to result in in a statistically significant increase in IELT as compared to placebo. Fluvoxamine was found not to be effective in significantly increasing IELT as compared to placebo. Side effects

reported in these studies were significant for decreased libido and even anejaculation.

Eight RCT's on licensed dosages of Dapoxetine taken on demand basis showed significant increase in IELT as compared to placebo (mean difference of 1.16 minutes (CI-0.94-1.39 minutes) for 30mg and 1.66 minutes (95% CI 1.46-1.87 minutes) for 60mg ($p<0.00001$), with 60mg clearly better than 30mg (mean difference 0.46 minutes, 95% CI 0.19 to 0.74 minutes; $p=0.0009$. There were similar benefits in ejaculatory control, sexual satisfaction and global impression of change and clinical benefit. Common side effects include diarrhoea, headache and dizziness which were largely dose dependent.

Thirteen RCT's on the use of Clomipramine (oral or nasal) showed poorly reported data on benefit in increase in IELT as compared to placebo. Inhaled Clomipramine 4mg showed a mean difference of 1.68minutes, 95% CI-1.06-2.29 minutes; ($p<0.00001$) as compared to placebo. Dry mouth, constipation and local irritation to the inhaled preparation were common side effects reported.

Twelve RCT's on Phosphodiesterase inhibitors showed poorly reported mixed results with Vardenafil and Tadalafil significantly increasing the IELT but Sildenafil failing to show any significant increase in IELT as compared to placebo. Common side effects include flushing, headache and palpitations.

Evidence for alpha blockers (2 RCTs), Tramadol (7 RCT's), Acupuncture (2 RCT's), Chinese medicine (5 RCT's), Delay devices (1 RCT), and Yoga (one Non-RCT) is limited and of poor methodological quality.

Justifying the need for this trial:

In India, the cost of intervention is largely born by the patient themselves, and in economies where the burden of therapeutic interventions are largely borne by the patient, cost becomes the major deciding factor for treatment initiation and continuation (147). Moreover, most men presenting to our hospital for the treatment of PE come alone and are unable to stay on for psychological or behavioral treatment, Hence, in most instances, drug treatment is preferred after some standard education and supportive sessions.

Dapoxetine is currently the only drug licensed specifically for the treatment of PE. However the data from the dapoxetine trials need to be interpreted with caution. Whilst there is no generally agreed minimum clinically important change in IELT, Pryor et al. (53) concluded that a change in ejaculatory latency of 1 minute would constitute a clinically meaningful change, based on a correlation of global impression of change scores with mean changes in IELT. In their pooled analysis, the improvement in mean 12-week IELT from baseline for the placebo group was 1 minute. In the pooled analysis, the difference between placebo and dapoxetine 30 mg for the improvement in mean 12-week IELT was 1.2 minutes. In both the pooled analysis and the individual studies, the difference between dapoxetine 30 mg and 60 mg 'on demand' for the mean IELT at 12 weeks was less than 1 minute (0.5 minutes for the pooled analysis). In the pooled analyses, the percentage of men who reported that their premature ejaculation was 'better' or 'much better', and who reported 'good' or 'very good' satisfaction with sexual intercourse and 'good' or 'very good' perceived control over ejaculation was

statistically significantly higher with dapoxetine 30 mg and 60 mg 'on demand' compared with placebo 'on demand' (all p<0.001,). However, the differences between the 30 mg and 60 mg strengths were small (and unlikely to be clinically important). In addition, the majority of men in the dapoxetine groups (69.3% in the 30 mg group and 61.7% in the 60 mg group) did not report that their PE was 'better' or 'much better' (53). Thus, the data from the Dapoxetine trials indicate a statistically significant benefit for Dapoxetine, but the clinical importance of these data, as assessed by the proportion of males with PE deriving a significant improvement in their satisfaction with their ejaculatory latency, is uncertain.

Dapoxetine is not without adverse effects. In the pooled analysis (148), adverse events occurred in 35.1% of men in the placebo groups, 47.0% in the dapoxetine 30 mg 'on demand' groups and 60.3% in the dapoxetine 60 mg 'on demand' groups. Across the groups approximately 3% of men reported severe adverse events and 1% or less of men reported serious adverse events. Across all 5 RCTs, syncope (including loss of consciousness) occurred in 0.05% of men in the placebo groups, 0.06% of men in the dapoxetine 30 mg groups and 0.23% of men in the dapoxetine 60 mg groups (no statistical analysis presented).

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) considered evidence on the benefit/risk balance of the 60 mg dose. Concerns had been raised that the benefit of 60 mg compared with 30 mg was considered too modest to outweigh the potentially increased risk for severe events of syncope. The CHMP concluded that while a statistically significant efficacy difference in favour of 60 mg compared with 30 mg had been established, the

mean (or median) difference in IELT between the 30 mg and 60 mg dose appears marginal. The CHMP concluded that based on IELT data as well as patient-and partner-reported outcome measures, around 12% more men respond to dapoxetine 30 mg compared with placebo and an additional 5–10% more men respond to the 60 mg dose compared with the 30 mg dose. However, the safety profile of the 60mg dose may not justify its routine use compared to the 30 mg dose.

Against this background, the rationale of conducting this study includes the following:

1. Daily drug therapy seems more preferred in PE compared to on demand therapy.

2. There have been no clinical trials comparing Clomipramine with Dapoxetine in the treatment of PE, Clomipramine is an affordable option with efficacy reported in over 60% of participants (135) (142) . The improvement with Dapoxetine from the trial evidence may not match this, and this needs a head to head trial.

3. Cost of Dapoxetine 30 mg is around 6 times of that of Clomipramine 25 mg and thrice that of 50 mg. However, clomipramine shows its best effect when used daily and this daily dose increases drug costs. Cost-effectiveness is considered a major deciding factor in deciding treatment options in a developing country like India.

Methodology

Design:

The study was designed as a pragmatic, randomized, parallel group, allocation-concealed, assessor-blinded, active-controlled trial.

Setting:

The study is currently ongoing and is being conducted in the Psychiatry, Andrology and Urology department outpatient services of a teaching general and multi-specialty referral hospital in south India.

Participants:

The study sample comprises 120 married adult men who presented with a diagnosis of premature ejaculation as a result of a non-organic etiology and fulfilling eligibility criteria and who provide written (and video-taped) informed consent for study participation.

Key criteria

a. Inclusion Criteria:

- Married male
- Has an active and stable sexual relationship with wife
- Age – 21 to 64 years
- Heterosexual orientation
- Speaks either of these languages – Hindi, Bengali, English, Tamil, Telugu
- Reports consistently ejaculating within one minute or less of vaginal penetration
- The problem has persisted for at least 6 months, and has been experienced 75%-100% of the time
- The problem results in clinically significant distress, sexual frustration, dissatisfaction or tension between partners
- This condition is not better accounted for by another non-sexual mental disorder, medication or illicit substance use, or medical condition
- Agrees to have sexual intercourse at least once a week (or at least six times) over the study period of six weeks
- Agrees not to use study medicines more than once a day

b. Exclusion Criteria:

- Comorbid major mental illness (Psychosis, Bipolar affective disorder, Major Depressive Disorder, Obsessive compulsive disorder)
- Active psychoactive substance use in dependence pattern (other than Nicotine)
- Uncontrolled or Untreated medical comorbidities (Diabetes, Hypertension, Hypothyroidism, Cardiac illness, renal disease)
- Current use of antipsychotic and antidepressant drugs, herbal medicines, phosphodiesterase type 5 inhibitors (for example, sildenafil).
- Use of either Dapoxetine or Clomipramine in the past
- Any potential neurological, urological, or endocrine cause of PE
- Scoring "3" or "4" on first three domains, and "4" on 4th domain of the Premature Ejaculation Profile (PEP)

Target sample size and rationale:

In a pooled analysis of 4 RCTs (148) comparing Dapoxetine versus placebo with outcome measures similar to our study, 26.2% of those given Dapoxetine 30 mg on demand reported "good" or "very good" perceived control over ejaculation and 37.9% reported "good" or "very good" satisfaction with intercourse. Overall 30.7% reported their PE was better or much better on the CGI-Change (148).

In the RCTs of Clomipramine compared to other SSRIs and placebo (8) that used similar outcome measures, ejaculatory control improved in 69.4% of participants given clomipramine, and 77.8% on clomipramine reported “good” or “very good” satisfaction with sexual intercourse.

Assuming the response to Dapoxetine 30 mg would be 38% and with clomipramine 50 mg would be 65%, the sample size calculation is as follows (149) (150).

The standard normal deviate for $\alpha = Z\alpha = 1.960$

The standard normal deviate for $\beta = Z\beta = 0.842$

Pooled proportion = $P = (q1*P1) + (q0*P0) = 0.515$

$A = Z\alpha\sqrt{P}\ (1-P)\ (1/q1 + 1/q0) = 1.959$

$B = Z\beta\sqrt{P1}\ (1-P1)\ (1/q1) + P0(1-P0)(1/q0) = 0.810$

$C = (P1-P0)2 = 0.073$

Total group size = $N = (A+B)\ 2/C = 105$

Continuity correction (added to N for Group 0) = $CC = 1/(q1 * |P1-P0|) = 7$

Sample size (with continuity correction) = 120 (60 in each group)

Intervention and Comparator agents:

Intervention –

Tab. Clomipramine 25 mg once daily in the evening for 1 week followed, if needed, by 50 mg once daily for 5 weeks (intercourse to occur at least once weekly or at least six times over six weeks)

Comparator –

Tab. Dapoxetine 30 mg 1-3 hour before intercourse, once weekly for 6 weeks (or if intercourse occurs more than once a week, for six doses)

Co-intervention:

All participants received a psychoeducation package for at least one session by consultant psychiatrists (Appendix 5)

Main outcome measures:

Primary outcome –

The primary outcome is the improvement of premature ejaculation at six weeks (or after the first six sexual encounters) to be measured by validated patient-reported measures –

1. The **Premature Ejaculation Profile (PEP)** that measures changes in the participants' subjective sense of control over ejaculation, satisfaction with sexual intercourse, distress related to PE, and interpersonal difficulty due to PE, and

2. Participant-reported **Clinical Global Impression of Change (CGI-C)**

1. **Premature Ejaculation Profile (PEP)** (Appendix 2)

The PEP is a 4-question patient-reported outcome that asks a respondent about –

1) His subjective sense of control over ejaculation,

2) Satisfaction with sexual intercourse

3) Distress related to PE, and

4) Interpersonal difficulty due to PE

Each question is answered on a 5-point Likert-type scale and an index score is derived by averaging the responses to the 4 questions. The PEP has been extensively employed in clinical trials and has good test-retest reliability and known groups' validity (127). The original validation of the PEP was based on the DSM-IV-TR PE criterion and a man is considered a premature ejaculator if his IELT was two min or less. The current DSM-5 includes an IELT time criterion of approximately one minute.

Measurement of improvement using PEP -

1. Domain 1 - Perceived control over ejaculation: Scores of 3 (Good) and 4 (Very good) will be taken as treatment success
2. Domain 2 - Satisfaction with sexual intercourse: As above
3. Domain 3 - Personal distress related to ejaculation: Scores of 3 (a little bit) and 4 (not at all) will be taken as success

4. Domain 4 - Interpersonal difficulty related to ejaculation: Scores of 4 (not at all) will be taken as success

In addition, an Index score will be calculated for each participant by averaging the scores on the four questions.

2. Clinical global impression of change (CGI - C) – (Appendix 3)

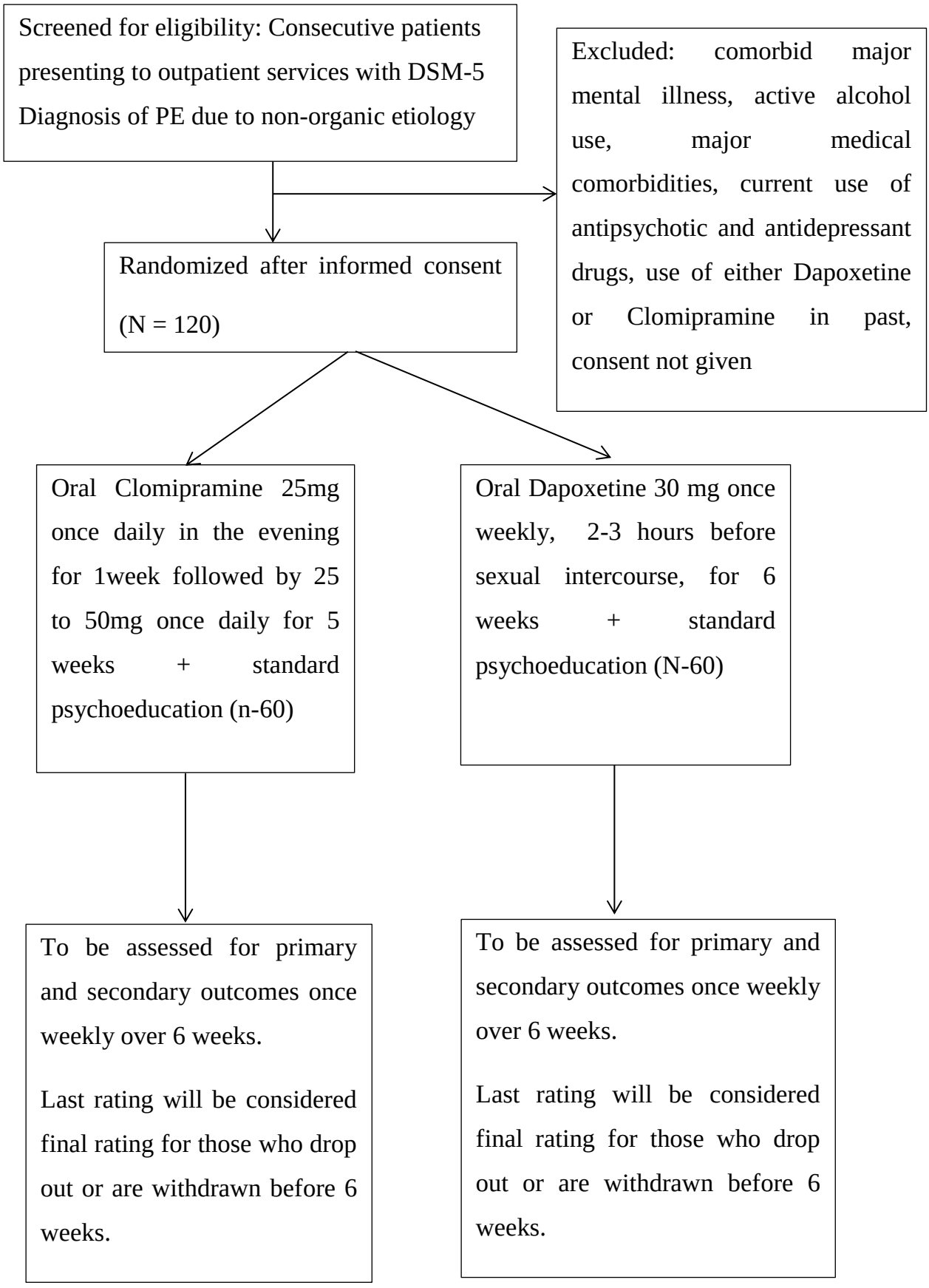
Patient reported rating scale: Scoring is done on a 7 point Likert-type scale- responses scored 2 (better) and 3 (much better) will be rated as clinically improved.

Secondary Outcome/s:

Secondary outcomes that are being assessed are adverse effects of the interventions using the validated side effects rating scale called the Antidepressant Side-Effect Checklist (ASEC - Appendix 4), and drug discontinuation rates (and reasons for discontinuation if known- e.g.: lack of efficacy, adverse events, etc).

Outcomes are being assessed weekly by the primary investigator (PI) who is blind to treatment allocation, by face to face interviews or by telephonic interviews or messages (SMS, email, WhatsApp) when participants return home before the end of the study according to participant's choice.

Diagrammatic algorithm of the study:



Method of randomization:

The randomization sequence was prepared by personnel not involved in the clinical management of participants, using computer generated randomization sequences with block sizes of 20. The randomization codes were sent to the pharmacist, and none of the study personnel involved in clinical assessments or care had access to this code until data entry and analysis is completed.

Method of allocation concealment:

The pharmacist packed interventions in serially numbered, sealed, opaque, plastic boxes, identical in appearance and weight. As determined by the randomization code, the boxes would contain 7 tablets of Clomipramine 25 mg for each of the six weeks of the study and an additional 35 tablets of Clomipramine 25 mg in sequentially arranged packets (for those in whom a higher dose (50 mg) is considered due to insufficient efficacy), or 6 tablets of Dapoxetine 30 mg. The interventions were packed in plastic and paper covers, and the boxes pre-tested to ensure that the interventions cannot be identified.

Once consent had been obtained from the patient for inclusion of the participant in the study, the treating doctor would send him to the pharmacist who would select the next consecutively numbered box from the pharmacy. The treating doctor would then break the seal (ensuring that the principal investigator (PI) is not present) and the patient would then be considered randomized. The treating team and the study investigators would be unaware of what intervention will be given to the participant until the sealed box is opened and the patient then

considered randomized to the intervention as per the randomization sequence. This concealment of allocation would ensure that selection bias is prevented.

Blinding and masking:

Since this is a pragmatic study where dosing schedule of the interventions are different, patients would not be blind to what treatment they are getting. Clinicians would also be aware of what treatments are being given so they can explain about the schedule to participants. However the PI of the study- DM will continue to be unaware of what intervention is administered; and will undertake blind ratings of the study's primary and secondary outcomes. This study would therefore be assessor blinded for primary and secondary outcomes and adverse events.

Phase of trial: Phase III

Date of first enrolment: 9th August (officially trial started) / 16th August (first patient recruited) 2017

Estimated duration of trial: 1 year from the date of starting recruitment of patients into the trial.

Post-Trial benefits and care:

All participants received usual standard care during and after the study, as determined by the treating clinical units. At the end of the trial, participants who found the study drug useful and wish to continue were prescribed the drug but had purchase them. This information was be specified in the information sheet for

obtaining consent. If they did not find the study drug useful, they were offered the option to try the other trial drug again to be purchased by prescription (or they will be offered other alternatives). The results of this trial are expected to provide evidence to inform practice in the management of people with premature ejaculation.

Statistical analyses:

Analyses were done by intention to treat, where the last recorded outcome has been used to impute their final outcome. The participants' dichotomized responses to the domains of the PEP and the CGI-C, and the frequency of adverse events and drug discontinuation rates was planned to be compared between interventions using relative risks and 95% confidence intervals (CI) as well as the risk difference with 95% CI. The mean difference with 95% CI in scores on the PEP index has also been compared between interventions. Additional analyses were done to evaluate the difference in changes from baseline on the PEP and CGI-C.

Statistical methods used for the primary outcome:

Categorical outcomes:

Efficacy –

The proportions showing improvement on the four domains of the PEP will be compared between on demand Dapoxetine and daily Clomipramine using absolute measures (risk difference) and relative measures (Relative risks), both

accompanied by their 95% Confidence Intervals (CI). The dichotomized CGI change score will also be similarly compared. These differences will be assessed for weekly ratings but the primary outcome would be differences in the 6-week rating.

If patients drop out or are withdrawn before the 6 week rating, the last observation carried forward (LOCF) method would be used, where the scores on the last assessment before withdrawal or drop out would be used to impute the final rating.

Safety –

The proportion of patients with any adverse event on the AESC scale as well as those with serious adverse events warranting discontinuation was similarly compared. Individual adverse events were compared and ranked by frequency.

Continuous outcomes: Efficacy-

The PEP index (the average score of the summed scores on each domain of the PEP) will compared between intervention groups using the independent sample t test and also assessed using the mean difference with 95% CI.

Methods for additional analyses -

The change from baseline to end of the trial in the domains of the PEP will also compared between interventions using absolute and relative measures (RD, RR) with their 95% CI. The proportions showing at least a change of 2 categories in the score in each domain of the PEP will also compared.

Results

The first patient was recruited on the 16th of August 2017 after the trial was registered prospectively with the CTRI (Registration no: CTRI/2017/09/009691).

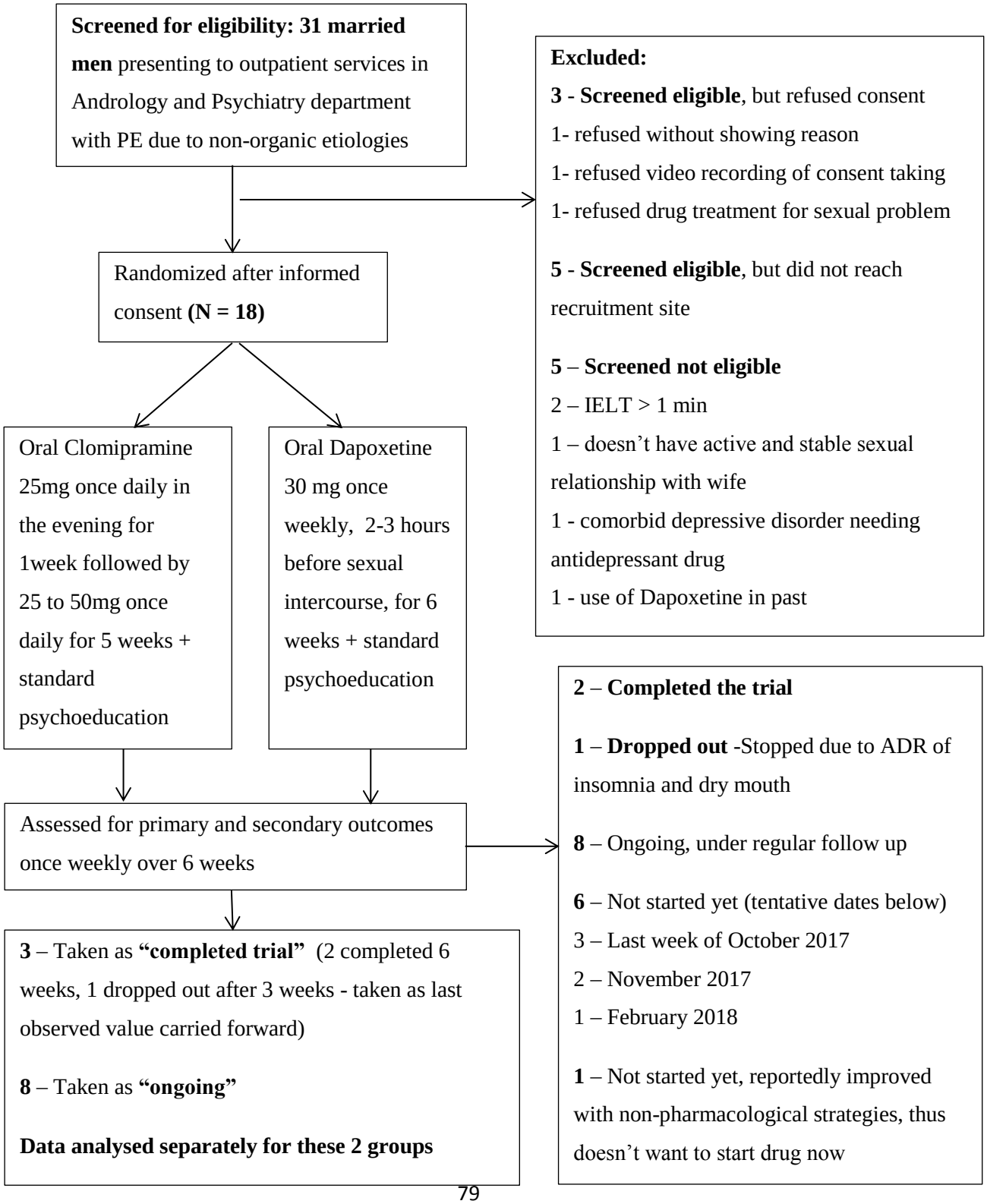
The trial is ongoing and we present here the results of the data analysis from the 18 patients who have been recruited into the trial till 13th of October 2017. This is not an interim analysis; we present the demographic profile, assessment of primary and secondary outcome measures of the 18 patients recruited without breaking the randomization code as the trial is ongoing. Only the data of the 3 patients (2 who have completed the trial and 1 who has dropped out of the trial due to side effects) have been analysed after having broken the code using Intention treat analysis; however we are able to analyse them descriptively without making any major inferences. The significance of the findings of their primary outcome measures (PEP profile at 6 weeks) and the CGI scores of these two patients was done calculating the difference in means (PEP Index score) and comparing them using the non-parametric equivalent of the independent sample t test of significance (Mann-Whitney U test) considering a non-normal distribution.

On breaking the Randomization code of these 3 patients, it was known that the 2 patients who completed the trial were in the Clomipramine arm and 1 patient who dropped out was in the dapoxetine arm.

The analysis of data of the 18 patients was done using descriptive statistics and the analysis of test of significance for the 3 patients (2 who completed the trial

and 1 who dropped out of treatment) was done using Non-parametric test of significance (the Mann-Whitney U test) using SPSS version 16.0.

Flowchart of the trial



Demographic characteristics of the study population

This section presents the analysis of the demographic variables and the baseline PEP scores and PEP Index score of all the 18 patients who were recruited in the study.

Of the 18 married male who gave written informed consent for the study, 11(61.1%) were below 40 years of age, 7 (38.2%) were above 40 years out of which 14 (77.8%) of them presented alone, only 4 (22.2%) came with wife.

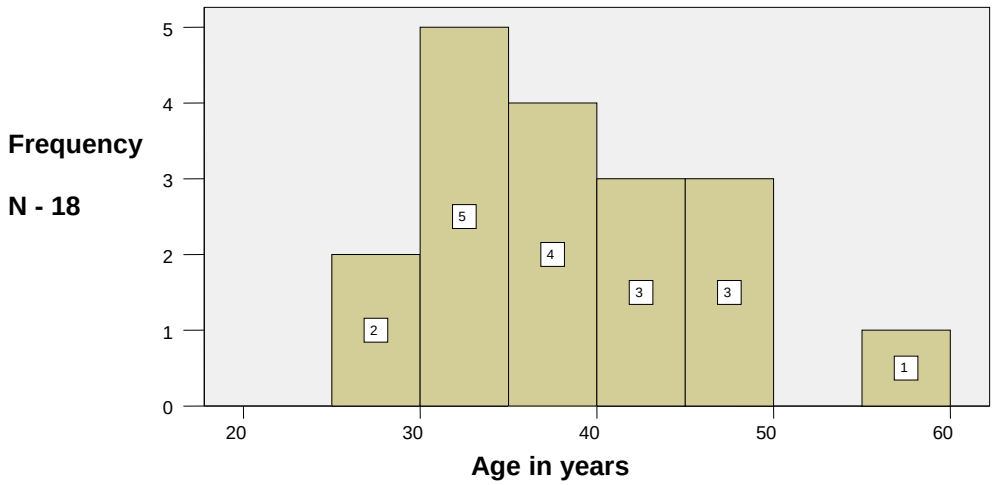


Figure 2 – Histogram showing Distribution of participants along different age groups

Highest educational qualification achieved is described below-

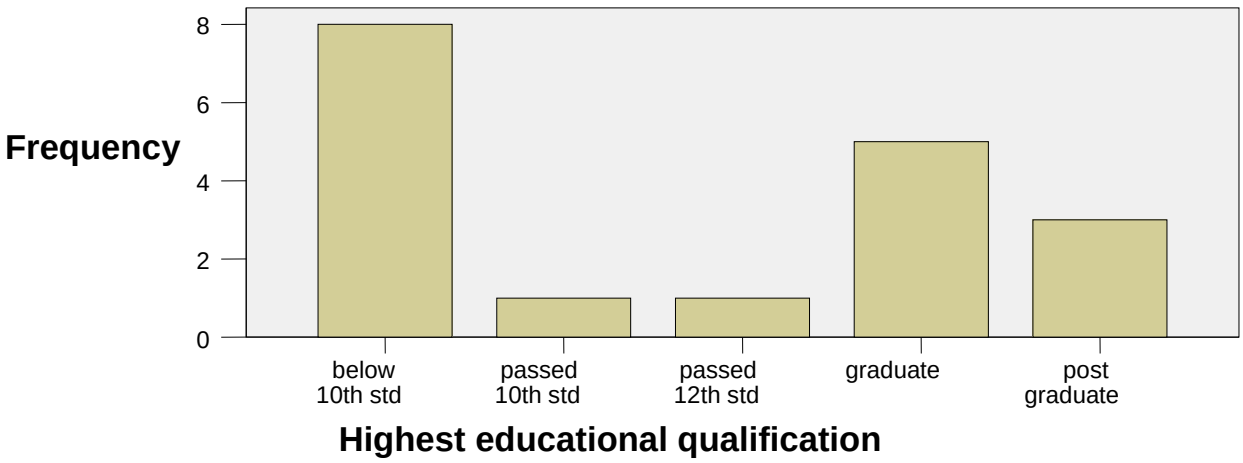
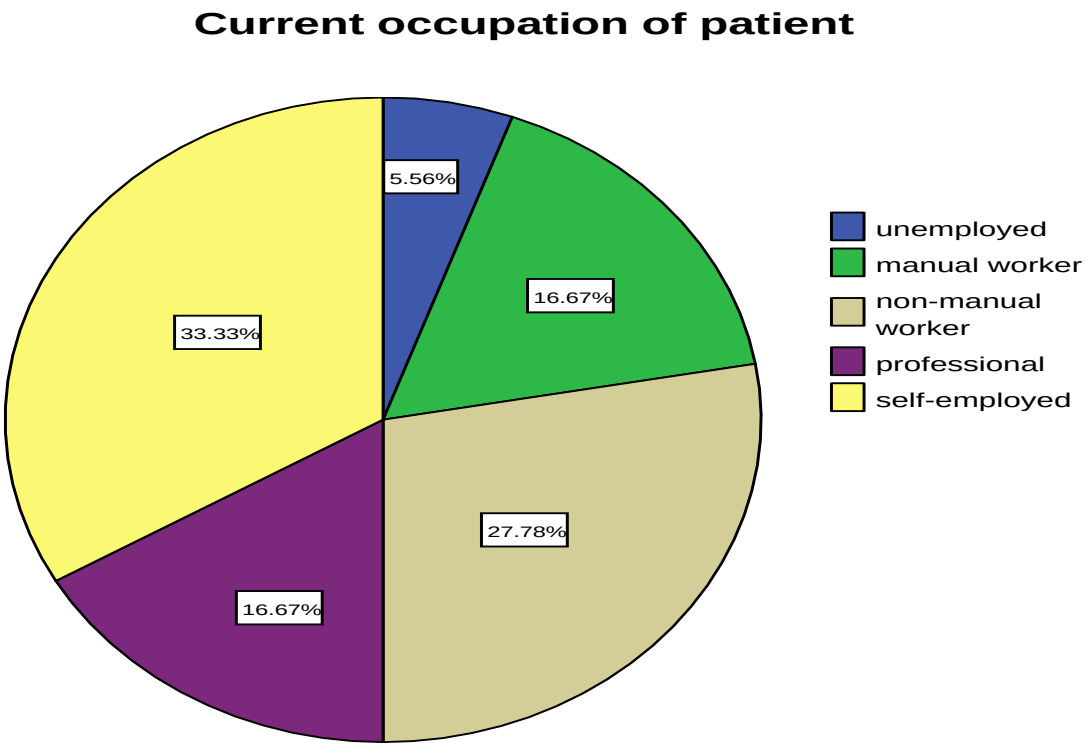
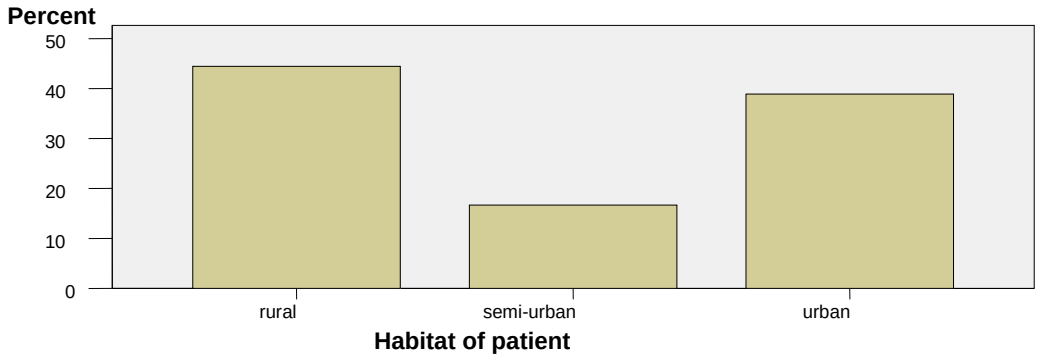


Figure 3 – Frequency Bar diagram showing highest educational level achieved

Distribution of current occupation is as follows (Figure 4)–

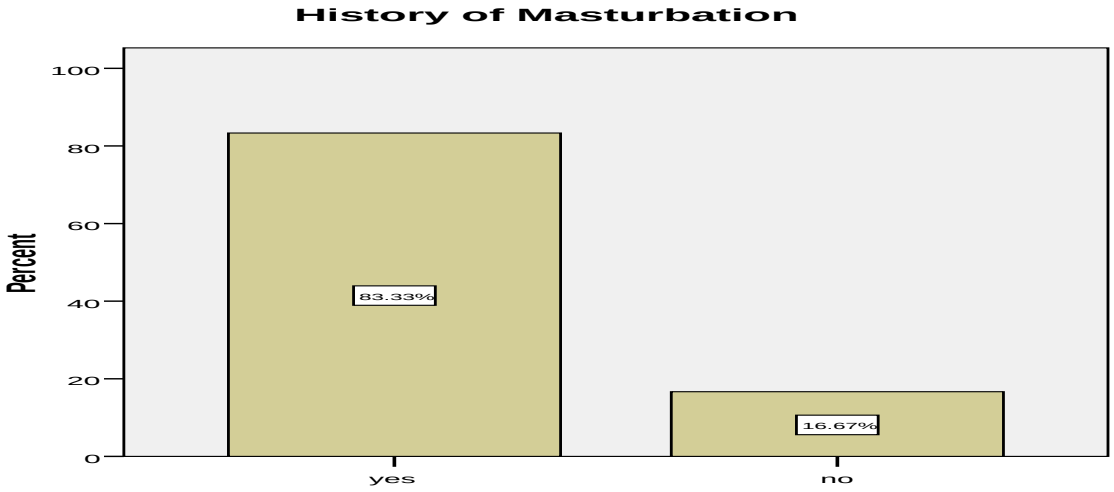


Majority were self-employed, whereas 5.56% were unemployed. Regarding socioeconomic status, – 13 (72.2%) comes from middle socio-economic status, 2 (11.1%) and 3 (16.7%) from lower and upper socio-economic status respectively. Habitat of patients is described below (Figure 5) –



10 (55.6%) of them were described as pre-morbidly well-adjusted, 8 (44.4%) reported to have anxious traits.

Clinical variables – 15 (83.3%) of the subjects reported having current or past masturbatory habit, whereas 3 (16.7%) denied masturbatory habit (Figure 6)-



Of all the participants having masturbatory habit, 12 (80%) reported guilt associated with it and 3 (20%) denied having any guilt.

Three (16.7%) participants reportedly had high risk sexual behaviour in the past such as having unprotected sexual intercourse with unknown or multiple partners, sexual encounter with commercial sex workers etc, whereas majority (83.33%) denied any such behaviour.

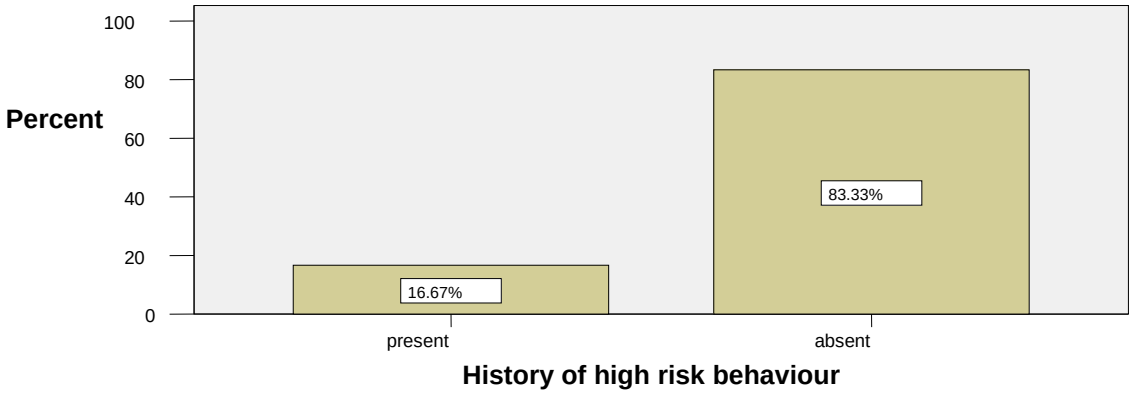


Figure 7 – Bar diagram showing high risk behaviour in the participants

Many common sexual misconceptions were found in 15(83.3%) of them, and multiple misconceptions were found in 10 (55.5%).

Commonest misconception involved their perception about size of penis.

(Described in table no 5 below) –

Sexual misconceptions	Frequency(N)	Percentage (%)
Size of penis	9	50.0
Density of semen	7	38.9
Weakness	7	38.9
Loss of semen	6	33.3
Shape of penis	4	22.2
Decrease in gland size	4	22.2
Impotence	3	16.7
Weight loss	1	5.6
Others	1	5.6
None	3	16.7

Average usual frequency of sexual intercourse ranged from 2 to 25 per month, with 8 of them reporting 10 or more intercourses per month.

Majority (16 participants) reported doing foreplay before coital act. Duration of foreplay ranged from 2 to 30 minutes, with 7 (43.8%) of them reported duration of 10 minutes or more. 12 (75%) of them reported that they enjoy foreplay, whereas 4 (25%) participants reported that they do not enjoy the act of foreplay, rather focus mainly on coital act.

Proportion of subjects with history of foreplay and attitude towards it are described below (figure 8, figure 9) –

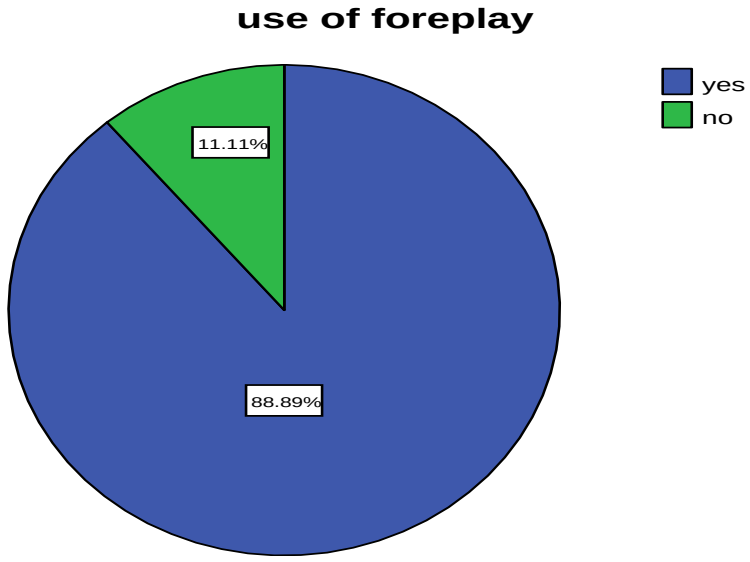
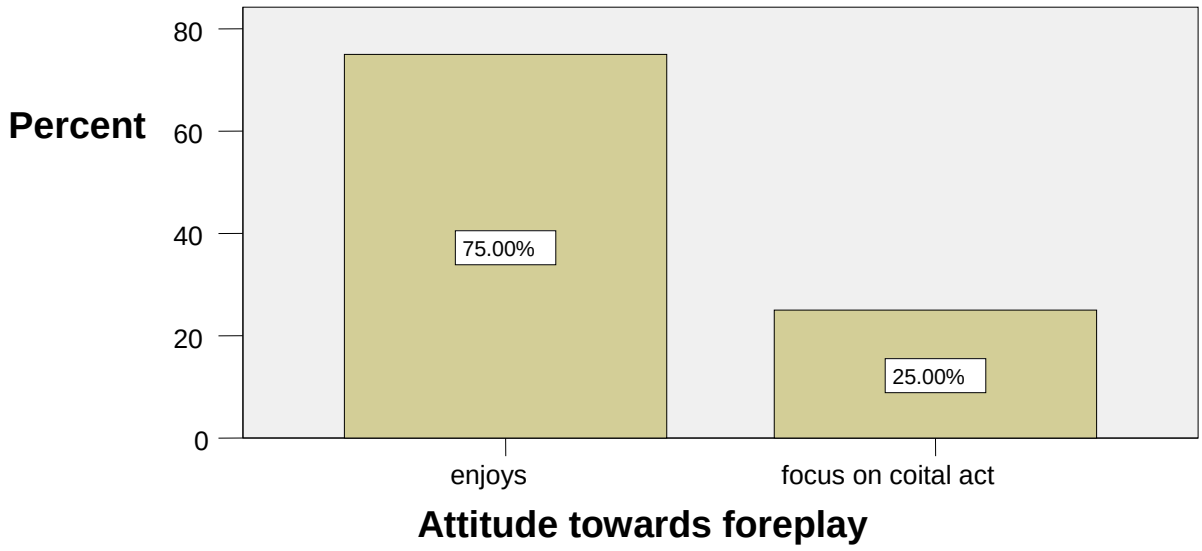


Figure 8 – Foreplay

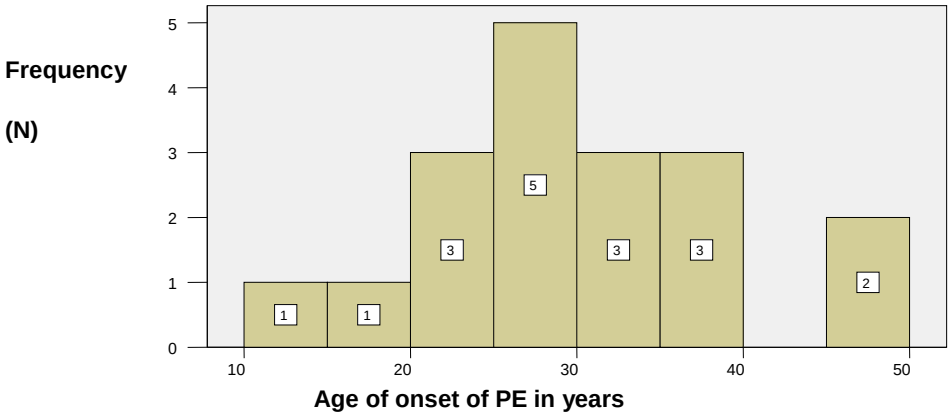
Figure 9- Attitude towards foreplay



Regarding use of condom during sexual intercourse, 3 (16.7%) reported regular use, 1 (5.6%) irregular use, and 14 (77.8%) no use.

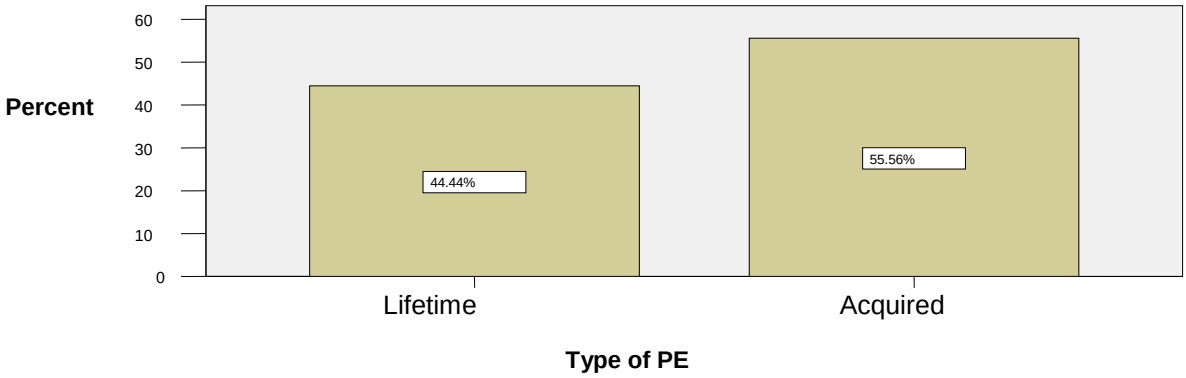
Correlates of PE – Age at onset of PE ranged from 14 years to 50 years, with 2 (11.1%) below 20 years, 8 (44.4%) in 20 -30 years, 6 (33.3%) in 30-40 years, 1 (5.6%) in 40-50 years and 1(5.6%) above 50 years age group.

Figure 10 - Age of Onset of PE



Duration of illness ranged from 12 to 264 months. 7 (38.9%) of them have been suffering from PE for 10years or more. Regarding subtype, 8(44.4%) reported Lifetime and 10(55.6%) reported acquired PE.

Figure 11 - Type of PE



Regarding severity of PE as defined by DSM 5 criteria- 12 (66.7%) reported mild, 2 (11.1%) moderate and 4 (22.2%) severe PE.

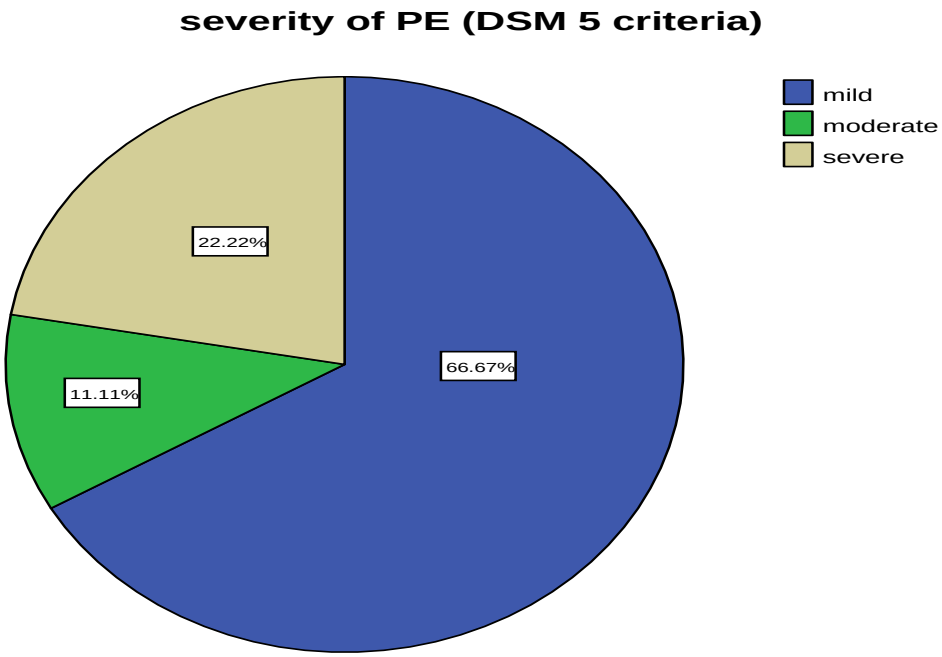
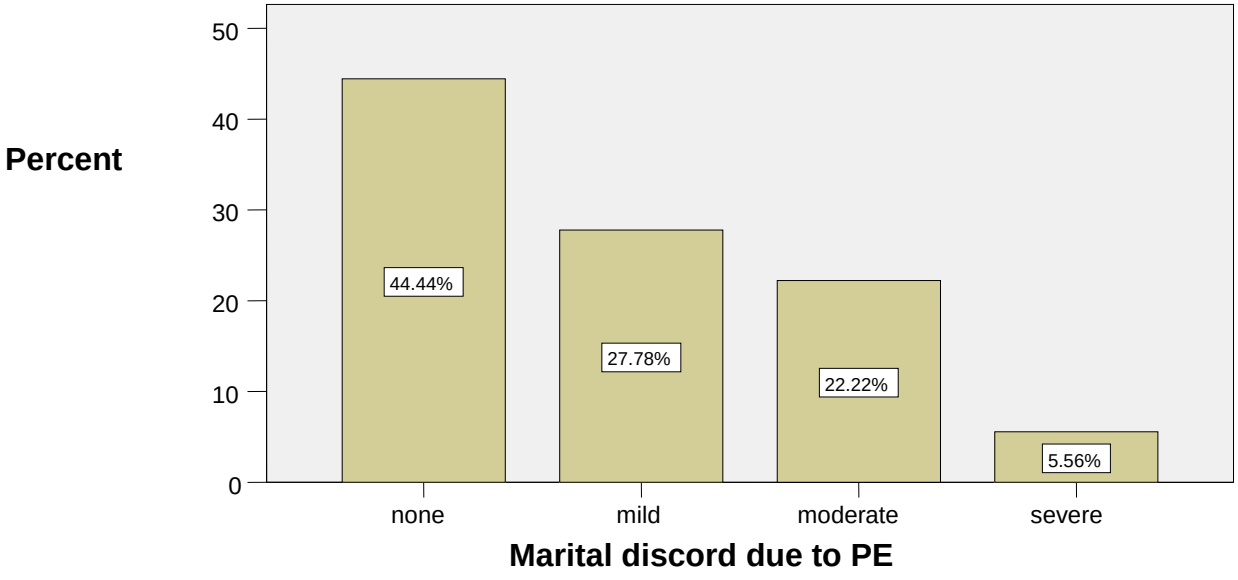


Figure 12 – Severity of PE

None of the participants had unconsummated marriage due to PE. However, 10 (55.6%) of them reported marital discord of varying severity. (Figure 13) –



Poor erection of penis was found in 5 (27.8%) patients with primary PE. Comorbid Dhat syndrome was found in 6 (33.3%) of them. 16 patients (88.9%) reported at least 1 attribution/explanatory model for PE, with 4 of them specifying multiple explanatory models. The commonest was “masturbatory act” (44.4%), followed by “loss of semen” (22.2%). (see table below) –

Table 6 – Explanatory model of PE

Explanatory model	Frequency	Percentage (%)
Masturbatory act	8	44.4
Semen loss	4	22.2
Aging	3	16.7
Sex at early age	2	11.1
Medication	2	11.1
Stress	1	5.6
Others	2	11.1
Don’t know/cant specify	2	11.1

Treatment history –

12 (66.7%) had received treatment before current trial, 6 (33.3%) were treatment naïve.

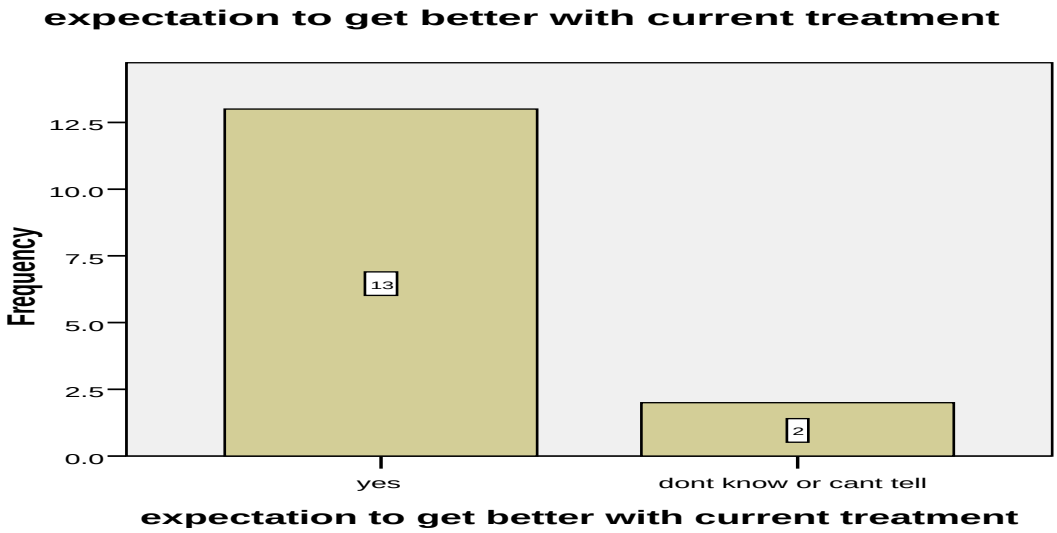
Types of treatment received is listed below -

Table 7 – Past treatment for PE-

Past treatment	Frequency	Percentage (%)
Medical	8	44.4
Ayurveda	6	33.3
Magico-religious	1	5.6
Others (Homeopath)	3	16.7

Number of doctors visited before current trial ranged from 1 to 12. Cost of past treatment ranged from INR 500 to 50,000, with 9 (75%) of them spending INR 10,000 or more.

When asked whether they think they will get better with treatment provided by the trial, 13 (72.22%) said “yes”. (Figure 14)



Baseline PEP Profile –

Primary outcome of this trial was improvement in PE, measured by the validated questionnaire “Premature Ejaculation Profile”.

It has 4 domains –

1. Perceived control over ejaculation
2. Satisfaction from sexual intercourse
3. Personal distress related to ejaculation
4. Interpersonal difficulty related to ejaculation

PEP baseline score - Perceived Control over Ejaculation (table 8)

Response	Frequency	Percentage
"Very poor"	11	61.1%
"Poor"	7	38.9%
Total	18	

PEP baseline score - Satisfaction from sexual intercourse (table 9)

Response	Frequency	Percentage
"Very poor"	7	38.9%
"Poor"	9	50%
"Fair"	2	11.1%

PEP baseline score - Personal distress related to ejaculation (table 10)

Response	Frequency	Percentage
“Extremely”	8	44.4%
“Quite a bit”	6	33.3%
“Moderately”	4	22.2%

PEP baseline score - Interpersonal difficulty related to ejaculation (table 11)

Response	Frequency	Percentage
“Extremely”	1	5.6%
“Quite a bit”	6	33.3%
“Moderately”	9	50%
“A little bit”	2	11.1%

PEP Index baseline score (table 12)–

PEP Index score	Frequency	Percentage
0.25	1	5.6
0.5	6	33.3
0.75	1	5.6
1.0	5	27.8
1.25	3	16.7
1.5	1	5.6
1.75	1	5.6

The analysis of the Primary outcome measure of at baseline showed 0.50 as the most frequent PEP Index score (in 6 patients-33.3%). 61.1% of the patients reported very poor control over ejaculation, 50% reported poor satisfaction from sexual intercourse and an equal percentage reported moderate difficulty in interpersonal relationship due to ejaculation.

Analysis of the PEP Profile at the end of 6 weeks—Primary Outcome Measure:

2 patients completed the trial between 16th August 2017 and 13th October 2017. One patient dropped out of the study at the end of 3rd week of the trial due to side effects of Insomnia and restlessness which were attributed by the patient to the medication. On breaking the code for these patients, the 2 patients who completed the trial were on Clomipramine and the 1 patient who dropped out at 3 weeks of the trial was on Dapoxetine. Analysis of these 3 patients was done on the basis of Intention to treat and the last observation carried forward (LOCF) was used to impute the findings of the drop out patient.

The primary outcome (Difference between the mean PEP score at the end of 6 weeks compared to the mean PEP score at baseline) was done using the non-parametric equivalent of the independent sample t test (Mann-Whitney U test). The mean Rank at baseline for the Clomipramine group was higher (2.25) than the dapoxetine group (1.50). However there was no difference in the mean rank of the PEP index scores at the end of 6 weeks (2.0).

The test statistics show no significant difference at baseline (U=0.5, p=0.480) and at 6 weeks (U=1, p=1.000) between the PEP index scores. This was expected considering the trial is ongoing and we had very few patients who completed the trial till the point of analysing the data.

The outcome for the CGI-S was categorically pre-decided as significant only if patients reach a score including and beyond 2 (“Better”). One patient who

completed the trial and who was on Clomipramine had a CGI-S of 2, the corresponding base-line score for this patient was 1. The rest of the 2 patients who were included in the analysis had a baseline score and a 6 week score of 1 ("Slightly better").

Secondary Outcome Measures: Side effect profile at the end of 6 weeks:

The side effect profile was assessed using the antidepressant side effect check list and the treatment discontinuation rate. Of the 3 patients, 1 patient dropped out of treatment because of side effects of dry mouth and insomnia which were attributed by the patient to the medication. The patient who dropped out was in dapoxetine arm of the trial.

One patient who completed the trial and was in the Clomipramine arm experienced drowsiness at the 2^{nd} week which improved in the subsequent weeks. The same patient experienced constipation from the 1^{st} to the 3^{rd} week of treatment which improved by the 6^{th} week of treatment. The two patients in the Clomipramine arm experienced side effects of sweating from 1^{st} to 3 week of treatment which again got better by the 6^{th} week of treatment. The patient who experienced constipation and drowsiness also complained of increased body temperature as a side effect attributed to the medication. Both the patients in the Clomipramine arm did not receive any treatment for the side effect and continued the medications in spite of these side effects.

Discussion

In this study we aimed to compare efficacy and adverse effects of oral Clomipramine versus oral Dapoxetine in married men presenting to Psychiatry, Urology and Andrology outpatient services with complaints of Premature Ejaculation due to non-organic etiologies meeting DSM 5 criteria. The trial, with a target sample size of 120, is ongoing. However, current analysis was done on data collected till 13th October 2017, during which 18 patient have been recruited and followed up.

From the reviewed literature, there are no past head to head trial between Clomipramine and Dapoxetine.

Summary of Results (Demographic data):

Of the 31 patients screened for eligibility in the outpatient departments, 26 patients were found eligible meeting the inclusion and exclusion criteria of the study. Out of these 26 patients, 5 patients did not reach the recruitment site (Department of Psychiatry which is 8km away from the Department of Andrology where they were found eligible) due to unknown reasons. Out of the 21, 3 patients (14.2%) refused informed consent (1 did not want the video recording, 1 refused because he did not want any drug treatment and 1 did not give any reason).

Of the 18 patients who gave video recorded written informed consent and who were randomized to either the Clomipramine or the Dapoxetine arm, 61.1% were below 40 years of age. Majority of them were from middle socioeconomic status

(72.2%), had studied below 10th standard (44.4%). The study subjects' habitat was almost equally distributed between urban and rural population which is similar to previous 2 previous epidemiological studies done in India. Premorbid personality was significant for anxious traits in 44.4% of the participants.

The patient population recruited in this study largely came alone (77.8%), were below 10th standard educated (43.4%), were self-employed (33.3%), came from a rural background (42.5%) and had pre-morbidly anxious personality traits (44.4%).

83.3% of the 18 patients had past history of masturbation, did not have any history of high risk behaviour (83.3%) and 80% of those who had such a history had masturbatory guilt. The patients harboured many misconceptions, the commonest amongst them was size of the penis (50%), low density of semen (38.9%) and an equal proportion experiences weakness (38.9%). The patients used foreplay (88.9%) and most of them enjoyed the foreplay (75%) rather than being performance driven.

Patients enrolled in the study had the onset of PE most commonly between the age of 20-30 years with a chronic history of acquired subtype of Premature Ejaculation (55.56%) with 66% having mild severity. Most patients expressed Masturbatory guilt to be the reason behind them having PE (44.4%).

Though, according to DSM-5 criteria, these patients had mild variety of PE, their premature ejaculation profile showed otherwise with 44.4% being extremely distressed with their premature ejaculation, 88.9% of these patients were

discontent with the quality of sexual intercourse and all of them felt loss of control over their ejaculation with 38.9% judging it as poor and 61.1% judging it as “very poor”.

Comparison with other studies:

The age group of the recruited patients in our study seems to be younger as compared to with mean age of sample in studies done in western countries using Clomipramine as is evident from Althof et al (139) where it was 38 years, Segraves et al 45.9 years (151), Waldinger et al 36.9 years (135).

Studies done using Dapoxetine in western countries showed mean age of 40.5 years in studies done by Pryor et al (53), 34 years - Safarinejad et al (144), 41.2 years – Kauffman et al (142) which again are age groups higher than those recruited in our study.

Epidemiological studies done on sexual dysfunction in India by Rao et al (55), Kalra et al (152) shows majority of patients are in 18-30 years age group though these studies were not RCTs.

The domains of masturbatory guilt and sexual misconceptions seems to be similar as compared to other descriptive studies done in India which describes masturbation in 42.6% of patients and guilt associated with it in 87.5% of them (92). In a study done in Mumbai by Kalra et al, rates of history of masturbation

were as high as 90% and guilt associated with it was evident in 56.7% of the recruited population (152).

Sexual misconceptions were found in 46.4% of patients presenting with complaints of PE in a study done in psychosexual clinic in Bangladesh (153) which is similar to those found in our study.

Regarding the type of Premature Ejaculation, Ratio of lifetime and acquired PE was 1:1.25 i.e. both subtype were almost equally present in the sample which studied 110 patients visiting a psychosexual clinic in Bangladesh which is quiet similar to the result of our study.

Data from previous studies show comorbid erectile problem in 28.5% (153), 24.7% (152), 21.9% (92), and comorbid Dhat syndrome in 68.4% (154), 13.8% (92) which are again similar to the findings of our study. Attribution of sexual problem was to “masturbation” in 52% which is similar to this study, and to “stress” in 14% (152) whereas only 1 subject (5.6%) reported “stress” as an attributing factor. The decreased percentage of co morbidity with Erectile dysfunction could be related to the younger age group profile in these studies and in ours; patients in older age group (41–50 years) suffered more with both PE and ED (42.9%) (152).

Regarding treatment history, in our study 33% never had treatment before, 33% had Ayurvedic, 5.6% magico-religious, and 44.4% had Allopathic drug treatment; and 75% of them spent INR 10,000 or more on treatment for PE in the past. In an Indian study done by Kalra et al in Mumbai (152), 52% were

treatment naïve, 31% had taken some alternative treatment for which included Ayurvedic and other herbal treatments, and only 17% had taken some allopathic treatment for the same. Though the authors of this study do not elaborate the setting in which this study was done, it is possible that the difference could be due to difference in sample characteristics in the two studies.

Issues with respect to the use of IELT for diagnosis in DSM 5 and the aspect of Patient reported outcomes (PRO's)-

In our study, with reference to DSM criteria regarding severity of PE, majority (66.7%) came under "mild" category, followed by "severe" (22.2%) and moderate (11.1%), but this classification is solely based on IELT. This is clearly divergent from the PEP profile of these 18 patients participating in the study which shows all patients expressing loss of control, a majority of them (88.9%) dissatisfied with their quality of sexual intercourse and 44.4% expressing being "extremely" distressed personally with their ejaculation during sexual intercourse and about 50% of them having moderate level of interpersonal difficulty due to their early ejaculation. Though it is too early to judge and our trial is ongoing, the results on the 18 patients does reflect on the diagnostic difficulties in using the DSM 5 criteria which may not be a true reflection of the degree of control, personal dissatisfaction, personal distress and interpersonal difficulty that goes along with Premature Ejaculation.

The FDA does propose the use of patient reported outcome (PRO) measures as an additional worthwhile tool in men with homosexual orientation in order to help diagnose variable and subjective PE. The FDA also opines on the limitations of the use of PROs as an adjunct to a detailed psychosexual history, partner perspectives and face to face discussions which give an in depth view of each man's personal perception regarding the impact of PE in his life (155).

Premature Ejaculation Profile: PEP Index scores and individual domain scores:

Our study on the 18 patients with DSM-5 diagnosis of Premature Ejaculation did show that 33.3% of the patients had a PEP score of 0.50 and about 27.8% had a score of 1. The PEP Index score is an average of all the 4 domains assessed while assessing the Premature Ejaculation profile. The index course can be used effectively for diagnostic purposes as it gives an overall view of the severity of the condition subsequent to which the researcher can focus on individual domains and thereby can be used as screeners for the diagnosis of PE.

Two large observational studies in USA and Europe did compare IELT scores with each domain of PEP and with PEP index score and found a significant association between the two at IELT scores which were between 2-5 minutes and more than 5 minutes with corresponding significant mean PEP index scores being 2.91 and 3. 41 in the USA study and 3.04 and 3.46 in the European study (127).

In the individual domain scores, Randomized controlled trial done in Canada comparing Dapoxetine vs Placebo on 736 men with DSM IV diagnosis of PE (142) used individual PEP domain scores as outcome measure. The advantage of such domain based outcome measure allows the research to look at each domain separately and their by assessment treatment response in each domain; as in this case, in the personal distress related to ejaculation, the "not at all" and a "little bit" scores in the Dapoxetine group increased to 54.3% from baseline of 5% of patients.

Summary of Results of the 2 patients who completed the trial and 1 patient who dropped out in the Individual domain scores and PEP index scores:

This study aimed to test the efficacy and safety of Clomipramine vs Dapoxetine in DSM-5 diagnosed patients with PE based on the PEP profile and their index scores. The study is ongoing and it is evident that the data is insufficient to make any inference at this point in time. However, the two patients who completed the trial were on Clomipramine and the one who dropped out of treatment was on dapoxetine. The reason for dropping out of treatment was persistent insomnia and dry mouth attributed to Dapoxetine by the third week of the trial. The analysis, done as LOCF in this patient was suggestive of an improvement from "very poor" control over ejaculation to "fair" control over ejaculation, "very poor" satisfaction with sexual intercourse to "fair" satisfaction with sexual intercourse, "quite a bit" distressed with ejaculation to "little bit" distressed with early

ejaculation and “quite a bit” interpersonal difficulty related to ejaculation to “moderate” difficulty in interpersonal difficulty related to ejaculation.

In the 2 patients who completed the trial and were on Clomipramine the following were the changes in the individual PEP domains:

Table 13: Comparison of responses of PEP domains in the 2 patients at baseline and at completion of the trial on Clomipramine:

PEP domains	Baseline patient 1	Baseline patient 2.	At 6 weeks. Patient 1. (dose 25mg)	At 6 week patient 2. (dose 50mg)
Control over ejaculation	Very poor	Very poor	Poor	good
Satisfaction with sexual intercourse	poor	Poor	Fair	good
Personal distress related to ejaculation	Extremely	Extremely	Quite a bit	A little bit
Interpersonal difficulty related to ejaculation	Quite a bit	Little bit	Quite a bit	A little bit

We did not do a statistical analysis of each domains because of paucity of numbers and clearly the difference would not be significant but it is evident that one patient of Clomipramine improved on the individual PEP domains. This is reflected in the CGI-S scores as well with this patient having a score of 2 from the baseline of 1 while the rest of the patients CGI-S remained unchanged.

The PEP Index score as compared to baseline changed in patient 1 from 0.50 to 1.25 and in patient 2 from 1.00 to 3.50.

The PEP Index score in the patient on Dapoxetine changed from 0.50 to 2.25. The difference however, was not statistically significant.

Safety of Clomipramine and Dapoxetine in patients:

Till the 20th of October no life threatening side effects were reported in any group. The patient who dropped out at 3 weeks and was on Dapoxetine attributed discontinuation to insomnia and dry mouth even though he felt some benefit in his premature ejaculation symptoms.

The 2 patients who completed the trial and were on Clomipramine (one was on 25mg and the other was on 50mg) reported constipation, drowsiness and increased body temperature which improved gradually as they continued to take Clomipramine and they did not seek any additional treatment for the same.

The side effect profile in both the patients were similar to those found in individual placebo controlled trials of both the drugs (142) (135) (156).

Strengths of the Study:

This pragmatic, Randomized, allocation concealed, assessor blinded controlled trial testing the efficacy and safety of as required 30mg dose of Dapoxetine compared to daily 25/50mg of Clomipramine in patients with DSM-5 diagnosis of Premature ejaculation is the first of head to head comparison between the two drugs. It uses a valid and reliable patient report outcome measure of PEP with its 4 domains of control over ejaculation, sexual satisfaction with intercourse, personal distress related to ejaculation and interpersonal difficulty related to ejaculation at baseline and after 6 weeks of the trial.

The PEP being the outcome measure makes this study a pragmatic real world study with greater generalizability of the findings.

The study, with its well defined inclusion an exclusion criteria does attempt to answer an answered question in sexual science research and the evidence generated from such a study is expected to benefit patients, clinicians as well as researchers.

Limitations of the study:

The study uses the DSM-5 criteria to diagnose Premature Ejaculation. The DSM-5 uses IELT as a measure to diagnose premature ejaculation. The patients included in the study were asked about the time it took to ejaculate while having a sexual intercourse and based on their responses, were included or excluded from the study. It is possible that the report of time to ejaculate is subjective and is subject to recall bias affected need to get help and be cured—this might have led to inclusion of variable PE into the study.

The study includes only married men with heterosexual orientation as its inclusion criteria-this essential excludes men who have premature ejaculation within same sex relationships and people who have subjective sense of loss of control over ejaculation while masturbation.

Though the study looks at marital disharmony due to premature ejaculation, The study does not allow for partner satisfaction as one of its outcome criteria—this might be very important in marital relationships and does allow premature ejaculation to be seen within the dyad rather than an individual construct.

The slower than expected recruitment in the study (N=18) has led to non-significant research findings while comparing the two groups, we do plan to continue the study till we recruit the expected sample size.

The baseline characteristics of participants till now does bring out various psychological issues closely related to Premature Ejaculation—sexual misconceptions, masturbatory guilt, anxious personality traits and attribution

models to premature ejaculation to name a few. Though the study design does include standard rapport building and psychoeducation protocol to be given to all patients, it is not tailored to the patients' needs and might not address these complex issues and might not be sufficient enough to address these deep rooted psychological domains of premature ejaculation.

Conclusions

This ongoing pragmatic, randomized, assessor blinded, allocation concealed controlled trial uses a standard methodological framework to answer a clinical relevant question about comparative efficacy of Clomipramine vs dapoxetine in patients with premature ejaculation. The baseline profile of patients recruited till now (N=18) shows that the recruited patients are young, less than 10th standard educated married adults, presenting mostly alone with acquired premature ejaculation, with very poor control over their ejaculation, poor satisfaction from their sexual intercourse, extremely distressed in relation to early ejaculation and experiencing moderate difficulty in interpersonal functioning due to premature ejaculation and have multiple sexual misconceptions-the most prominent being the size of the penis and a significant proportion of them have masturbatory guilt.

The PEP profile of the 3 patients, 2 on Clomipramine who have completed the study and 1 on dapoxetine who has dropped out of study due to side effects does point towards improvement post use of both these medications; however the results are not generalizable at this point in time till the entire sample size is recruited and the study completed.

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Appendix 1 –

Information sheet and invitation to participate in a research study

Title of the study: CLOMIPRAMINE VERSUS DAPOXETINE IN THE TREATMENT OF PREMATURE EJACULATION: A RANDOMIZED CONTROLLED TRIAL

Dear Sir,

My name is Debanjan Mandal. I am a doctor in this hospital and a Post-graduate trainee (MD Psychiatry). As part of my training for the MD degree, I, along with the doctors in this hospital, am conducting a study to find out the better treatment for men with Premature Ejaculation. I am being guided in this study by Dr Prathap Tharyan and Dr Sumail Dholakia from Psychiatry Unit II.

I will first explain the important points about this study briefly and then seek your permission to let us include you in this study.

I will answer any questions you may have and then ask you to sign a consent form giving us this permission. I will also give you this information sheet (in English, Hindi, Bengali, Tamil, Telugu or Malayalam) that explains the points I have told you.

I shall also use a video camera to record the discussion I shall have with you, because that is the rule that the government has made about taking permission from patients or their relatives to take part in research studies. This video recording will be kept confidential and will not be revealed to anybody other than

government regulatory agencies (if they request it). The study has been approved by the research and ethics committee of the Christian Medical College, Vellore.

Your decision on whether you will or will not participate is entirely up to you. Whether you decide to take part or not take part in this study will not affect the treatment you will receive at this hospital

There are few important points you need to know to help you understand what this study is about.-

1. WHAT IS PREMATURE EJACULATION?

Premature Ejaculation (PE) is a common sexual problem in men. It is a condition where a man releases semen too early during sexual intercourse (often before or very shortly after intercourse starts). It has also been called early ejaculation, rapid ejaculation, rapid climax, premature climax. This results in emotional and relationship distress to the person and/or the couple. Men with PE often describe feeling that they have less control over release of semen, and avoid pursuing sexual relationships because of PE-related embarrassment. Premature ejaculation is an important cause for dissatisfaction in married life. You are being invited to participate in this study because your complaints indicate that you have premature or early ejaculation.

1. WHAT ARE THE TREATMENT OPTIONS FOR THIS CONDITION?

Drugs and counselling are found to be useful to treat this problem. In people who have early ejaculation that has been present for a long time and where ejaculation

occurs before or very shortly after intercourse starts, drug treatment along with some counselling is preferred to counselling alone. There are many drugs that can be used in treating this condition. Clomipramine and Dapoxetine are among the drugs (medicines) that are used widely for treatment of this condition but it is not clear which of these two drugs is more effective and has less side effects.

2. WHAT WILL BE DONE AS A PART OF THIS STUDY?

In our study, we want to compare the effects of Clomipramine versus Dapoxetine on the improvement of premature ejaculation. We also want to compare the side effects of these drugs. We hope to include120 men with PE in this study and half of them (60 men) will get Clomipramine and the other half (60 men) will get Dapoxetine. . If you agree to participate in this study, you will get one of the study medicines (Clomipramine or Dapoxetine) free of cost for the duration of the study. Additionally, you will receive counselling on how to improve the condition. If you take part, you will be expected to: 1. Take the study medicine strictly as advised; 2. Have sexual intercourse with your wife at least once a week for six weeks or on six occasions over the six week period of the trial; 3. Report weekly using a study form that we will give to you on your condition (which includes improvement in ejaculation as well as any side effects), in a manner that is described below and agreed upon between you and your doctor. 4. Agree to <u>not</u> take more than the prescribed dose of medicines and avoid other medicines other than those approved by your doctor.

At the end of study the benefits of the treatment and the side effects will be assessed and compared between the 60 men ho got Clomipramine and the 60 men who got Dapoxetine.

4. WHICH OF THE STUDY MEDICINES WILL YOU GET?

In studies like this one that compares the effects of two medicines, one reason why one of the medicines may appear to be better or not as good as the other is because the doctor selected the people into the study in a particular way so that those selected people who got the one of the medicines were either more ill or less ill at the start of the study, than the people who got the other medicine. This will result in differences in their effects that are not due to the medicine itself but due to differences in the severity of the illness or due to other factors. Therefore it is important to make sure that the effects of the medicines we are comparing are clearly due to the medicines themselves and not due to other reasons. The method used to be sure of this is to choose the medicine to be given to each person by a coded system similar to a lottery, or like tossing a coin. This method is called randomization and will help to make sure that everybody in the research study has an equal chance of getting either medicine. The doctor does not directly decide what treatment the patient gets and the patient cannot choose whether he gets a particular medicine.

In our study we are dividing the patients in to two groups using this process of randomization. One group will receive Clomipramine, and the other group will receive Dapoxetine. If you decide to participate, in this study, neither you or your

treating doctors will know beforehand which drug you will receive as this will be decided by the lottery. Once you have been told which medicine you will get, your doctor will then discuss with you how you should take the medicine.

5. WHAT WILL HAPPEN IF YOU ARE SELECTED TO TAKE CLOMIPRAMINE?

If you are selected by the lottery to get clomipramine, you will be given a box containing all the clomipramine tablets you may need for the six weeks of the study. You will be expected to take one tablet (which contains 25 mg of Clomipramine) daily between 7 and 8 pm with a glass of water for the first week. During this first week you are required to have sexual intercourse with your wife at least once. At the end of the week, I (Dr. Debanjan) and your treating doctor will contact you by phone. I will enquire about your improvement using a study form that we will give to you in the language of your choice. Based on this interview, your doctor will discuss with you the dose of Clomipramine you should take for the next five weeks, which might be 25 mg, if the response to treatment is satisfactory or it could be 50 mg (two tablets of 25 mg) daily, if the response to 25 mg is not satisfactory. The total duration of treatment for this study will be 6 weeks and you will be required to have sexual intercourse with your wife once a week during this time. If you decide to have sexual intercourse more frequently, we will assess the effect of the treatment after 6 such attempts. You will be asked to fill the study form before the treatment starts and then once a week till the end of the study (six weeks or six attempts at sexual intercourse if this happens more frequently than once a week). Your responses to the study

form can be communicated to me via either email, sms, WhatsApp, telephone (when I call you) or in person, as is convenient; and we will discuss your preferred method of keeping us informed of your progress.

5. WHAT WILL HAPPEN IF YOU ARE SELECTED TO TAKE DAPOXETINE?

If you are selected by the lottery to get Dapoxetine, you will be given a box that contains 6 doses of Dapoxetine (30 mg). This medicine is not to be daily but only on the days you plan to have sexual intercourse. On that day you should take one 30 mg tablet of Dapoxetine with a glass of water one to three hours before the time that you plan to have sexual intercourse. You should not take more than one dose of Dapoxetine on a single day. You are expected to have sexual intercourse with your wife six times during the six weeks of the study (within one to three hours of taking Dapoxetine). This could occur once a week for the six weeks. If you decide to have sexual intercourse more frequently, we will assess the effect of the treatment after 6 such attempts. You will be asked to fill the study form before the treatment starts and then once a week till the end of the study (six weeks or six attempts at sexual intercourse if this happens more frequently than once a week). Your responses to the study form can be communicated to me via either email, sms, WhatsApp, telephone (when I call you) or in person, as is convenient; and we will discuss your preferred method of keeping us informed of your progress.

6. WHAT ARE THE BENEFITS OF TAKING PART IN THIS STUDY?

Since both medicines are being used in clinical practice for the treatment of PE, the benefit with either of the medicines will be similar to what would happen if you were not taking part in a study but were getting either of the medicines as part of routine clinical care. People who benefit for these medicines report a delay in the time taken to ejaculate, more control of their ejaculation, less distress due to PE and the men and their wives report more satisfaction with sex.

7. WHAT ARE THE RISKS OF TAKING PART IN THIS STUDY?

As explained above, the risks of taking part in this study are similar to the risks of taking either of the two medicines during routine clinical care. The side effects of both of the medicines are well known and are mostly mild and temporary. Your treating doctor will advise you on how to minimise them at the start of the study. If you experience any side effect, please inform us during the weekly assessments.

One common side effect with Clomipramine is drowsiness in the initial weeks of the study, but this usually becomes less with time. Other common side effects include dry mouth, constipation, and giddiness (especially if you get up from the sitting of lying position too quickly). These side effects may be mild with 25 mg and more frequent with 50 mg of Clomipramine. Side effects of Dapoxetine 30 mg are nausea, loose motion and giddiness, and these are also usually mild and temporary. Very occasionally some people on Dapoxetine may experience more severe giddiness and if this occurs, you are requested to lie down with your legs

elevated above your body till this feeling passes. We will systematically ask you if you are experiencing any side effects using the study form every week. If these side effects occur and are troublesome or do not settle with continuing the medicine, we will discuss stopping the medicine with you. We will continue to provide care for your condition even if you were advised to stop the medicine.

8. ARE THERE ANY ADDITIONAL COSTS THAT YOU WILL PAY DURING THIS STUDY?

You will be provided study medicines free of cost for the duration of the study. All other costs related to registration and consultation fees will be according to the arrangements you have with your treating doctors. If there are any costs incurred by in providing us the weekly progress reports (phone calls, sms usage, internet costs), then this will be reimbursed to you or given to you in advance.

9. WHAT WILL HAPPEN AFTER THE STUDY PERIOD?

If you wish to continue the study medicine that you received after the six weeks of the study, we will prescribe that for you and you will have to purchase it from local medical stores. If you did not find the study medicine to be useful or if you found the side effects difficult to tolerate, then your doctor will discuss other medicines that you could use, including the study medicine that you did not receive, but you will be expected to purchase them from local medical stores (or from our pharmacy if you are able to). If you were getting concessional treatment from this hospital for consultations or medicines, then this concessional treatment will continue after the study period.

10. WILL THE INFORMATION ABOUT MY PARTICIPATION IN THIS STUDY BE KEPT CONFIDENTIAL?

By agreeing to take part you are also agreeing for the information we get from the study to be used in publishing the results of this study, but your personal details will be kept confidential and they will not be identified, as we will give them a code number. Names and other details will be known only to yor treating doctor and one or two people doing this study, but will be kept locked away from others.

11. CONSENT TO VIDEO-RECORD THE CONSENT INTERVIEW

As per the Government of India, you will also be required to let us video-record your consent to permit us to include you in this study. This is to record that we have taken proper permission before we did this study. This video recording will also be kept locked and will not be shown to others, unless the government requests us to show it to them for any reason.

If you have any doubts or want additional information please contact me-

Dr.Debanjan Mandal, Department of Psychiatry, Christian Medical College,

Bagayam, Vellore, Tamil Nadu – 632002

Mobile no.– 09597488363

Phone – 0416 228 4520

If you wish, I can also arrange for you to talk to Professor Prathap Tharyan, or Dr. Saumil Dholakia, who are guiding me in this research study.

Appendix 2 – **PREMATURE EJACULATION PROFILE (PEP)**

Domain	**Question**	**Scores & response options**
Perceived control over Ejaculation	'Over the past month, how was your control over ejaculation during sexual intercourse:'	0: Very poor 1: Poor 2: Fair 3: Good 4: Very good
Satisfaction with sexual intercourse	'Over the past month, how was your satisfaction with sexual intercourse:'	0: Very poor 1: Poor 2: Fair 3: Good 4: Very good
Personal distress related to ejaculation	'Over the past month, how distressed were you by how fast you ejaculated during sexual intercourse?'	0: Extremely 1: Quite a bit 2: Moderately 3: A little bit 4: Not at all
Interpersonal difficulty related to ejaculation	'Over the past month, to what extent did how fast you ejaculated during sexual intercourse cause difficulty in your relationship with your partner?'	0: Extremely 1: Quite a bit 2: Moderately 3: A little bit 4: Not at all

Appendix 3 –

Clinical Global Impression of Change (CGI) score -

Domain	**Question**	**Scores and response options**
Change in PE	‘Compared to the start of the study, would you describe your premature ejaculation problem as:’	−3: Much worse −2: Worse −1: Slightly worse 0: No change 1: Slightly better 2: Better 3: Much better

Appendix 4 - <u>The Antidepressant Side-Effect Checklist (ASEC)</u> –

Please score the following list of symptom 0=absent,1=mild,2=moderate,3=severe

Please indicate if the symptom is likely to be side-effect of medication(Y=yes, N=no)

Serial no.	Symptom	Score	Linked to medication?	
1	Dry mouth		Y	N
2	Drowsiness		Y	N
3	Insomnia (difficulty sleeping)		Y	N
4	Blurred vision		Y	N
5	Headache		Y	N
6	Constipation		Y	N
7	Diarrhoea		Y	N
8	Increased appetite		Y	N
9	Decreased appetite		Y	N
10	Nausea or vomiting (1= slight nausea, 2 = more nausea, 3 = with vomiting)		Y	N
11	Problems with urination		Y	N
12	Problems with sexual function		Y	N
13	Palpitations		Y	N
14	Feeling light-headed on standing		Y	N
15	Feeling like the room is spinning		Y	N
16	Sweating		Y	N
17	Increased body temperature		Y	N
18	Tremor		Y	N
19	Disorientation		Y	N
20	Yawning		Y	N
21	Weight gain		Y	N

Q1: What other symptoms have you had since commencing the medication that you think may be side-effects of the medication?

Q2: Have you had any treatment for a side-effect?

Q3: Has any side-effect led to you discontinuing the medication?

Appendix 5 –

Structured psychoeducation / psychotherapy module–

1. To establish rapport

2. To explore –

- Sexual knowledge, attitude, practice
- Sexual misconceptions
- Model of illness – biological / psychological/ religious / others

3. To Psychoeducate –

- Basic anatomy and physiology about sexual organs
- Stages of sexual cycle
- To address Sexual misconceptions and to reassure (tailored)

- About PE –

✓ Prevalence(it's a common sexual dysfunction)
✓ Etiological factors - biological / psychological
✓ Treatment modalities –
Pharmacological / Modifying the non-pharmacological factors

- Modifying the non-pharmacological factors –

✓ To shift the focus to pleasure from performance
✓ To reduce anxiety (follow general relaxation techniques)
✓ To reduce spectatoring
✓ To reduce performance anxiety
✓ To understand the concept of reaching orgasm simultaneously (with partner)
✓ To increase / improve foreplay
✓ Sensate focus (shift focus from ejaculation)