三軍總醫院 Tri-Service General Hospital

Premature Ejaculation Overview
早洩簡介

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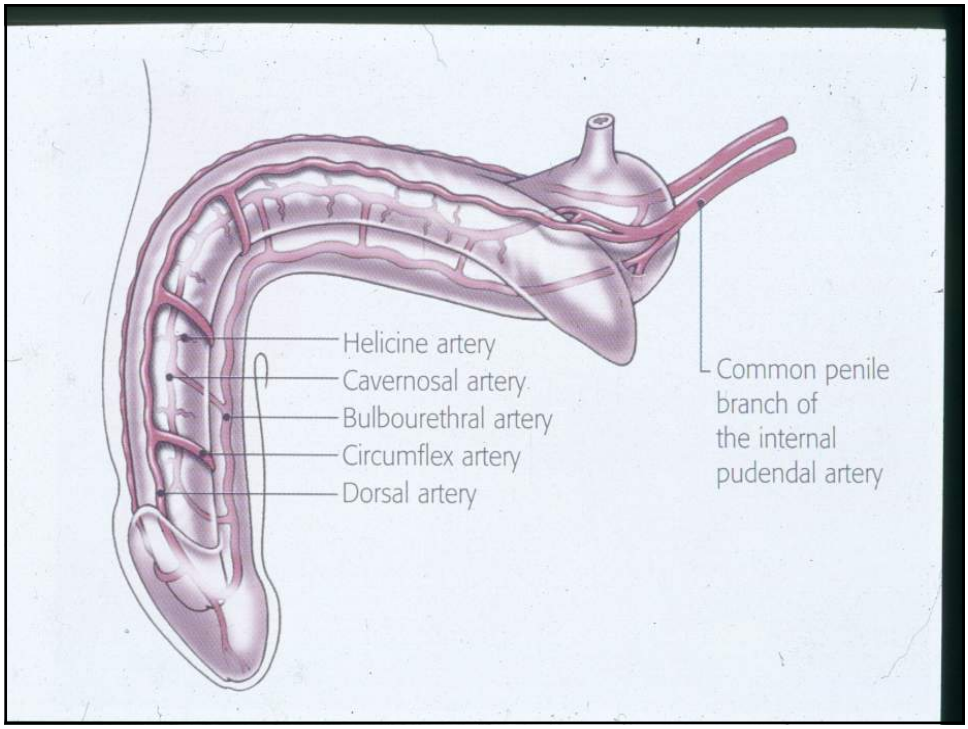
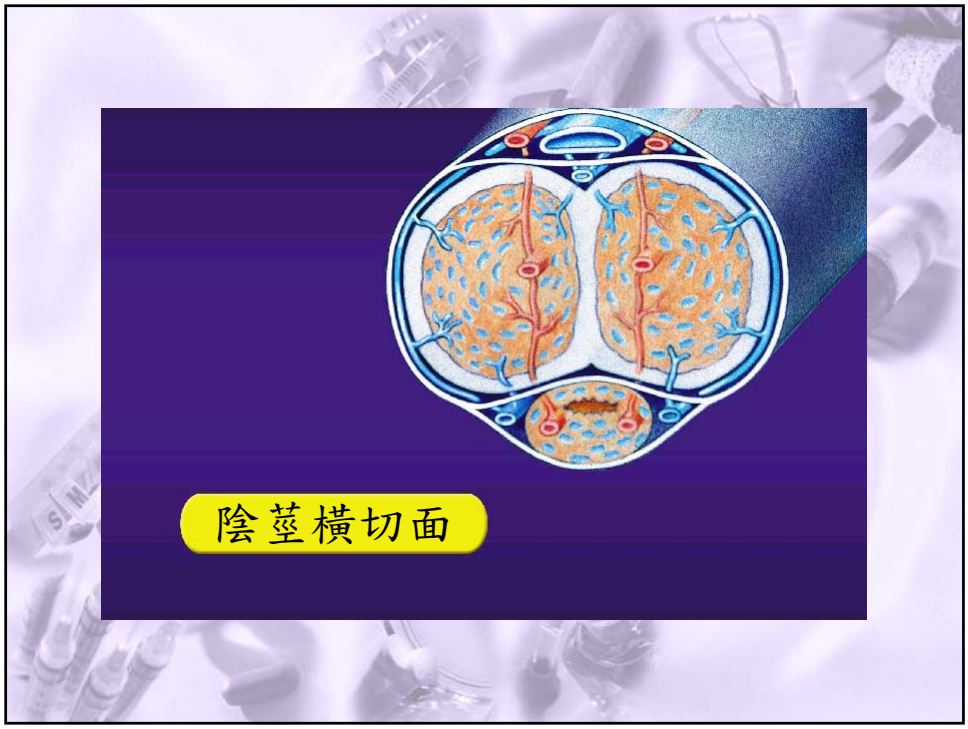
References

- AUA Update Series 2007 (Volume 26)
- **Premature ejaculation: current and future treatments.** Asian J Androl 2008 Jan; 10:102-109
- Guidelines on Male Sexual Dysfunction-Erectile Dysfunction and Premature Ejaculation. Euro. Uro 2010 Feb; 57:804-814.
- Considerations for an Evidence-Based Definition of Premature Ejaculation in the DSM-V. J Sex Med 2010 Feb; 7: 672-689.

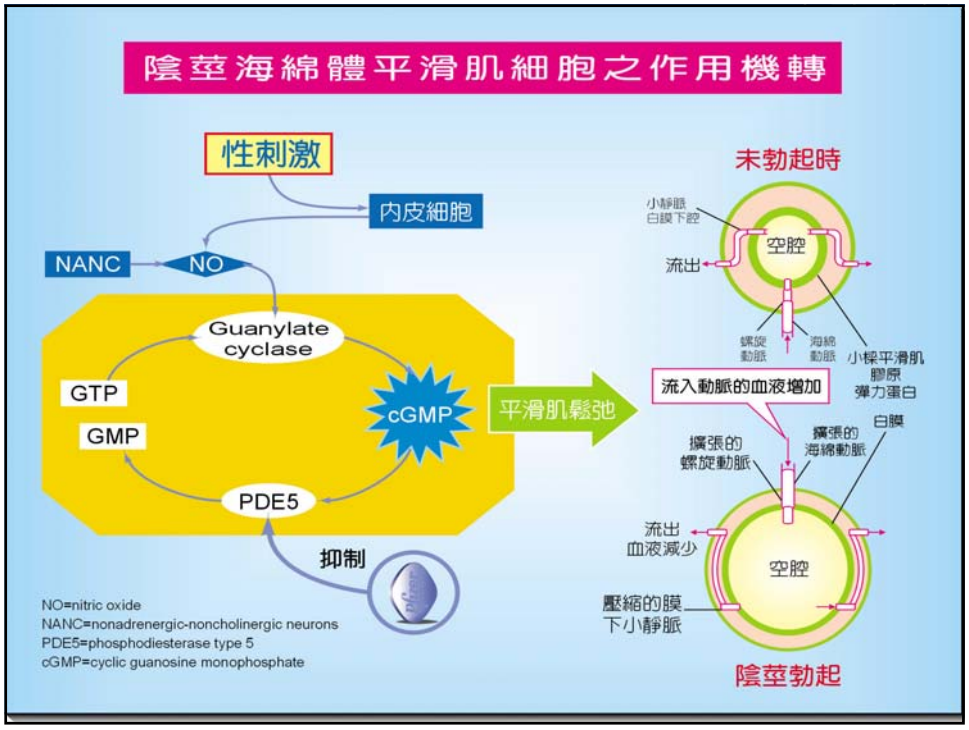

Helicine artery
Cavernosal artery
Bulbourethral artery
Circumflex artery
Dorsal artery
Common penile branch of the internal pudendal artery


陰莖橫切面

勃起是如何引起？

勃起時的神經傳導

性刺激(精神, 接觸) →分泌氧化物質→陰莖海綿體平滑肌和動脈擴張→勃起



勃起時陰莖的變化情形?

- 動脈的擴張
- 陰莖海綿體中平滑肌的擴張
- 減少靜脈血液的輸出

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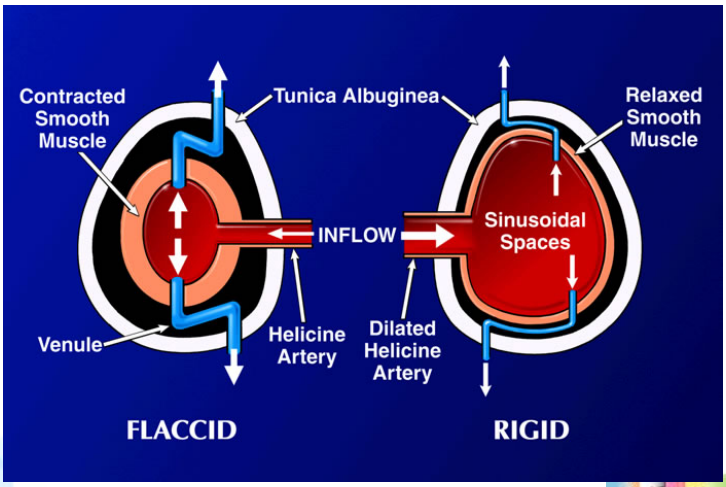
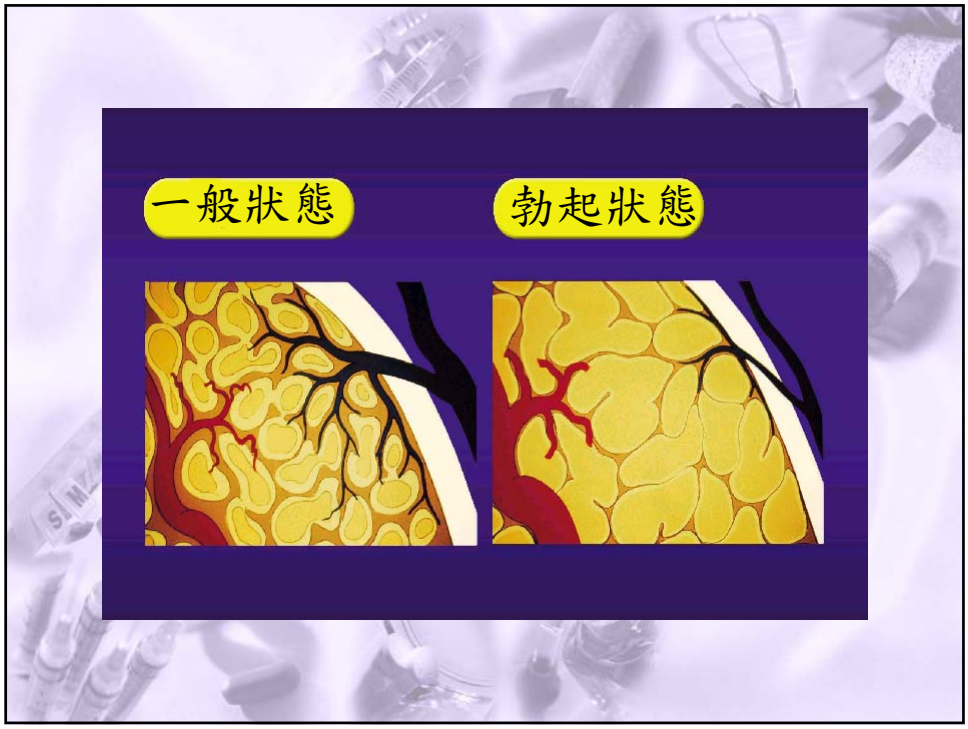
Diagram of penile erection





Physiology of Ejaculation

- Emission
- Expulsion
- Orgasm

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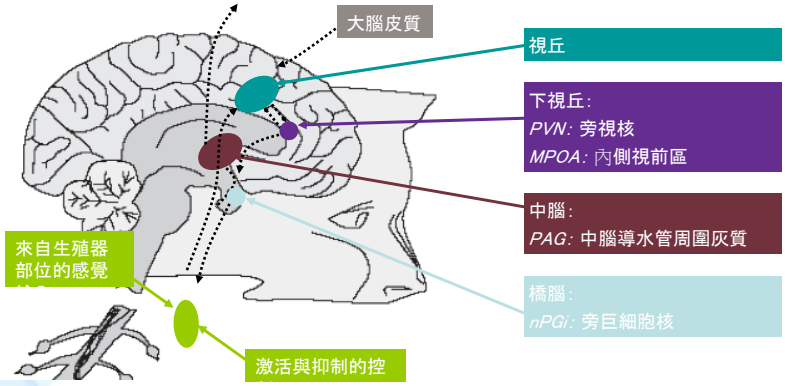
射精的神經控制脊髓以上的關鍵中心

射精的主要關鍵區域位於以下大腦各部位：



Giuliano & Clement (2006) Eur Urol 50(3):454–466

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Neurophysiology of Ejaculation

- Hypothalamus→ sup. hypogastric plexus → hypogastric nerve → seminal vesicle, vas deferens, prostate, bladder neck
- Pudendal nerve → bulbocavernosus, ischiocavernous and pubococcygeus muscle

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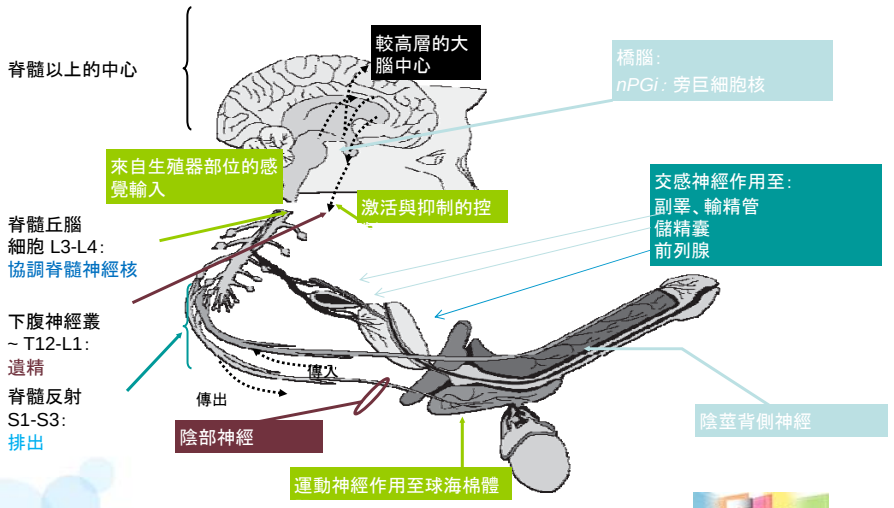
射精的神經生理學



Giuliano & Clement (2005) Ann Rev Sex Res 16:190–216

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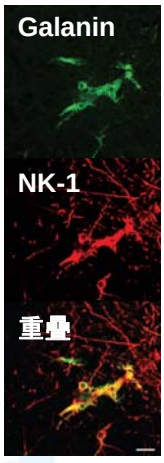
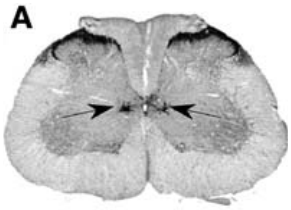
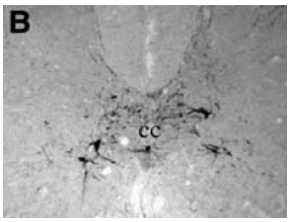
脊髓射精發動器(Spinal Ejaculation Generator, LSt)







- 集合激發射精所需的感官輸入
- 協調交感、副交感和肢體神經的輸出，引起遺精和排出

NK-1神經激素-1

擷取自 Truitt & Coolen (2002) Science 297:1566-1569

Emission

- Deposition of sperm into the posterior urethra
- The bladder neck contracts before emission to prevent retrograde ejaculation.
- A sympathetic response controlled by the spinal cord between the T10 and L2 level.
- Distention of the posterior urethra provides the sensation of ejaculatory inevitability.

Expulsion

- Forcible antegrade propulsion of semen from the urethral meatus.
- Contraction of the periurethral and pelvic floor muscles is coordinated with relaxation of the external sphincter.
- Expulsion is induced by neural signals that originate via afferent sensory stimuli from the genitals that are transmitted by the pudendal nerve to the spinal cord and higher centers in the brain.

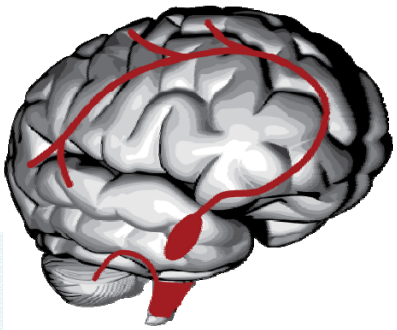
Orgasm

- Follows there lease of pressure in the posterior urethra.
- Cerebral processing of the afferent sensory stimuli results in the sensation of orgasm.
- However, orgasm is more complex than a sensory motor reflex as many mental and physical stimuli influence this event.
- Detumescence of the erection follows orgasm along with a refractory period during which the erectile response is blunted.

神經傳導物質在射精扮演的角色

•下列神經傳導物質有參與洩精(emission)
與射精(ejaculation)的過程:

- Serotonin (5-HT, 血清素)
- Dopamine (DA, 多巴胺)
- Gamma-aminobutyric acid (GABA, γ-胺基丁酸)
- Noradrenaline(正腎上腺素)
- Serotonin 被認為是射精過程中最主要的一個神經傳導物質
  - 多重serotonin 接受器在下視丘,腦幹和脊隨



McMahon et al, Disorders of orgasm and ejaculation in men. In Sexual Medicine: Sexual dysfunctions in men and women. 2nd International Consultation on Sexual Dysfunctions, Paris, 2004; Donatucci (2006) J Sex Med 3(suppl 4):303–308

5-hydroxytryptamine (5-HT)

- An inhibitory role on sexual behavior
- High concentrations of central 5-HT will delay or interfere with ejaculation via activation of the post synaptic 5-HT2C receptors.
- Conversely,5-HT antagonists that lower central 5-HT create a hyperexcitable state similar to PE.

Serotonin

- Serotonergic neurotransmission has a complex feedback mechanism that help stomaintain 5-HT concentration with in the synaptic cleft.
- A short-term increase in serotonin release results in receptor modification of the presynaptic neuron as a feedback mechanism to reduce serotonin release.
- Serotonin in the synaptic cleft activates 5-HT1A and 5-HT1B receptors on the presynaptic neuron which decrease nerve firing and there lease of serotonin. In addition, removal of serotonin from the cleft is also accomplished by serotonin transporters at the presynaptic endings and in serotonergic cell bodies.
- Therefore, any serotonergic neurotransmission has a complex feedback mechanism that pharmacologic therapies designed to increase serotonin levels must also be able to resist the homeostatic tendencies of the serotonin neurons.

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血清素在動物性行為中扮演的角色

- 1960 年代開始的臨床前研究顯示，血清素 (5-HT) 與雄性大鼠的性行為有關
- 一般假設中樞血清素 (5-HT) 在雄性大鼠性行為的神經控制中，扮演著抑制性角色

Koe & Weismann (1966) Pharmacol Exp Ther 154:499-516; Ahlenius et al.(1971) Psychopharmacologia 20:383-388; Salis & Dewsbury (1971) Nature 232:400-401; Södersten et al.(1976) Pharmacol Biochem.Behav 5:319-327; Larsson et al.(1978) Brain Res141:293-303; Giuliano (2007) Trends Neurosci 30(2):79-84

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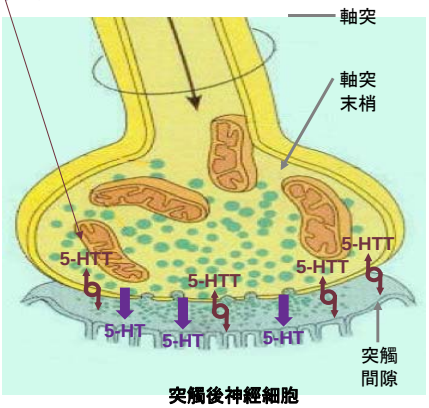
選擇性血清素再吸收抑制劑 (SSRI) 增加突觸間隙中的血清素含量

- 血清素神經傳導是由血清素轉運體 (5-HTT) 再吸收系統於原位調節
- 當血清素釋出，轉運系統便活化，移除突觸間隙的血清素，避免過度刺激突觸後血清素受體
- SSRI 抑制血清素轉運系統，增加突觸間隙中的血清素含量



5-HTT = 血清素轉運系統(serotonin transporter system)
5-HT = 血清素(Serotonin)

Giuliano (2007) Trends Neurosci. 30(2):79–84;
擷取自 McMahon et al (2004) Disorders of orgasm and ejaculation in men.In Sexual Medicine:Sexual dysfunctions in men and women.2nd International Consultation on Sexual Dysfunctions, Paris

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早期觀察 SSRI 對射精的角色 — 血清素的影響

- 服用抗憂鬱選擇性血清素再吸收抑制 (SSRI) 藥物，可能帶來性行為方面的副作用，包括射精延遲
- 早期試驗顯示，以不同 SSRI 每日給藥，確實可改善 PE 症狀[1]，例如：
  - 每日給藥 SSRI paroxetine，與安慰劑相比，臨床改善較佳[2]
  - 每日給藥 fluoxetine，與安慰劑相比，增加陰道內射精前驅時間 (IELT)[3]
  - 對於 IELT ≤ 1 分鐘的男性，每日給藥 paroxetine、fluoxetine 和 sertraline，與安慰劑相比，IELT 與基準點相較有所增加[4]
    - 對於接受 paroxetine 治療、IELT ≥1 分鐘的男性患者，IELT 也有類似增加[4]

1. McMahon (2005) Nat Clin Prac Urol 2(9):426-433; 2. Waldinger et al.(1994) Am J Psychiatry 151(9):1377-1379; 3. Kara et al.(1996) J Urol.156(5):1631-2; 4. Waldinger et al.(1998) J Clin Psychopharmacol. 18(4):274-281

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射精反應

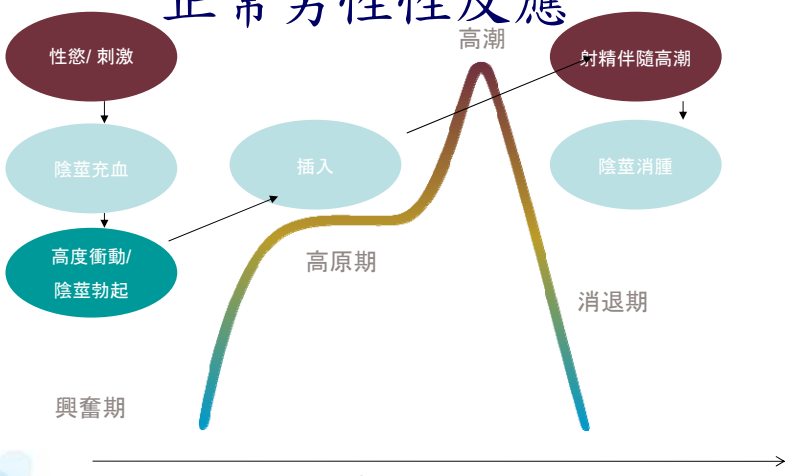
- 射精為經由一群脊髓內細胞，即脊髓射精發生因子，所調控的一種反射[1]
- 射精反應受到大腦中較高層中心控制[2]
- 血清素與血清素活化途徑，為傳達大腦所發出射精訊號的關鍵[3]
- 若 CNS 中血清素含量增加，會延後射精[4]

1. Truitt & Coolen (2002) Science 30;297:1566-1569
2. Giuliano & Clement (2006) Eur Urol 50(3):454–466
3. McMahon CG et al, Disorders of orgasm and ejacula tion in men.In Sexual Medicine:Sexual dysfunctions in men and women.2nd International Consultation on Sexual Dysfunctions, Paris, 2004
4. Giuliano F (2007) Trends Neurosci 30(2):79-84

Ejaculatory problems

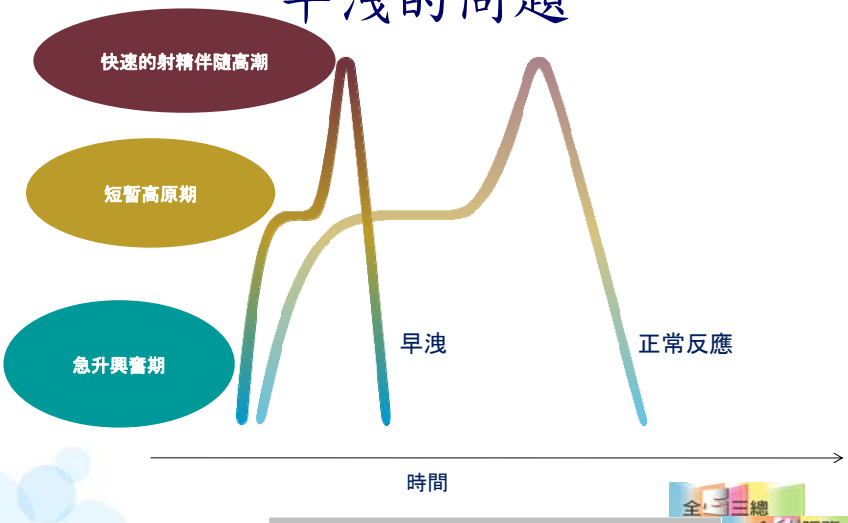
- **Premature ejaculation**
- **Retarded ejaculation**
- **Retrograde ejaculation**

正常男性性反應



Adapted from Donatucci (2006) J Sex Med 3(suppl 4):303–308

早洩的問題



Adapted from Donatucci (2006) J Sex Med 3(suppl 4):303–308

早洩

常見的男性性功能障礙

文獻中指出，約有 30% 的男性主述有早洩的問題

尋求治療的比例很低

流行病學並沒有完全建立

男性性健康忽略的領域以及未滿足的治療需求

Rosen (2000) Curr Psychiatr Rep 2:189-195; Laumann et al (1999) JAMA 281:537-544; Spector & Carey (1990) Arch Sex Behav 19:389-408; Porst et al.(2007) Eur Urology 51:816-824

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Premature ejaculation

- Most common male sexual disorder
- Incidence rate: 20-30%
- The prevalence of PE was not affected by age, marital status or race/ethnicity
- Often coexist with ED (36% ED patients had concomitant PE)

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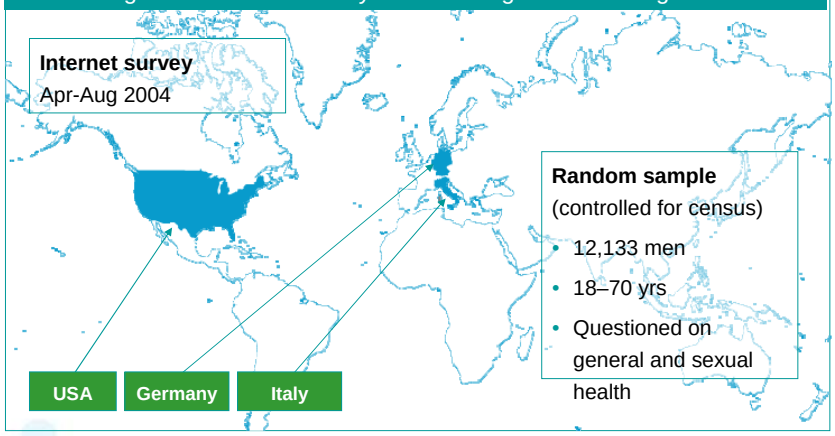
Premature ejaculation perceptions and attitudes (PEPA) study background

Largest international study to date designed to investigate PE



PEPA: Premature ejaculation perceptions and attitudes

Porst et al. (2007) Eur Urol 51:816–824

PEPA Study: 早洩定義

Analysis designed to conform as closely as possible to DSM-IV-TR criteria: 藍色的部分則定義為早洩

- **您認為您在性行為時控制射精的能力…？”**
- “差”
- “普通”
- “好”
- “很好”
- “極佳”

+

- **下列四個說明哪一個最能描述您從進入陰道到高潮的時間長度對您的人際關係影響…”**
- “對我是問題,但我的伴侶沒有這個問題”
- “對我是沒有問題,但對我的伴侶是個問題”
- “對我和我的伴侶都是問題”
- “對我和我的伴侶都沒有問題”

PEPA: Premature ejaculation perceptions and attitudes

Porst et al. (2007) Eur Urol 51:816–824

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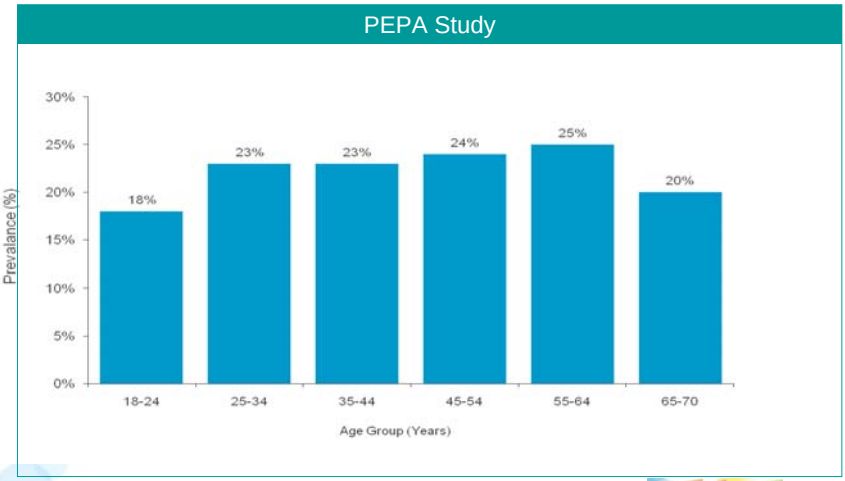
早洩盛行率在各年齡層皆一致



PEPA: Premature ejaculation perceptions and attitudes

Porst et al. (2007) Eur Urol 51:816–824

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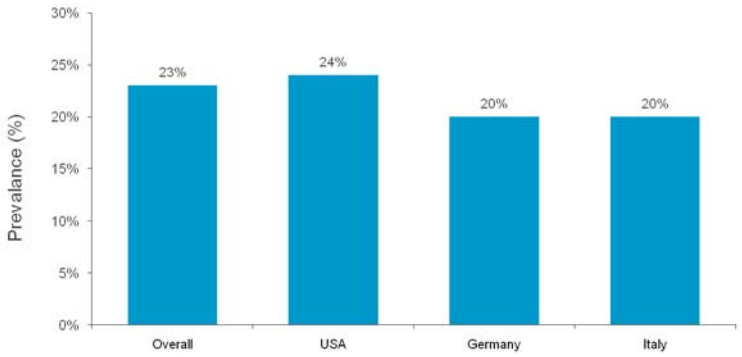
各個國家的早洩盛行率都相似

PEPA Study



PEPA: Premature ejaculation perceptions and attitudes

Porst et al. (2007) Eur Urol 51:816–824

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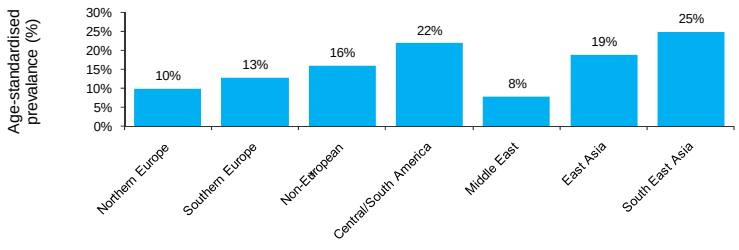
早洩盛行率在世界各區域也相似

"在前一年，您有過提早射精且持續兩個月以上的經驗嗎?"



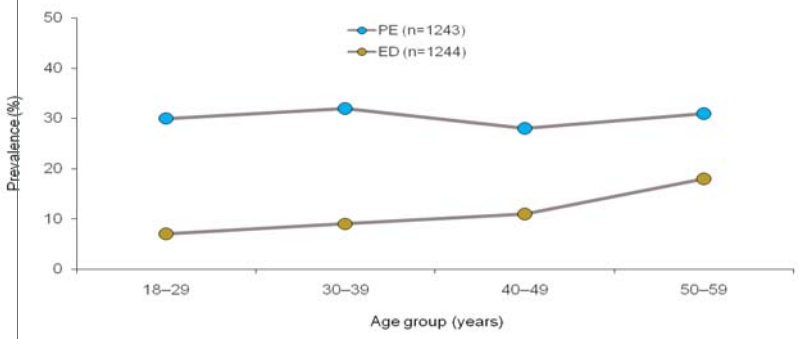
*USA, Canada, South Africa, Australia and New Zealand

PEPA: Premature ejaculation perceptions and attitudes

Nicolosi et al. (2004) Urology 64(5):991-997

早洩(PE)的盛行率比勃起障礙(ED)高且在60 歲以下的年齡層都一致

National Health and Social Life Survey analysis

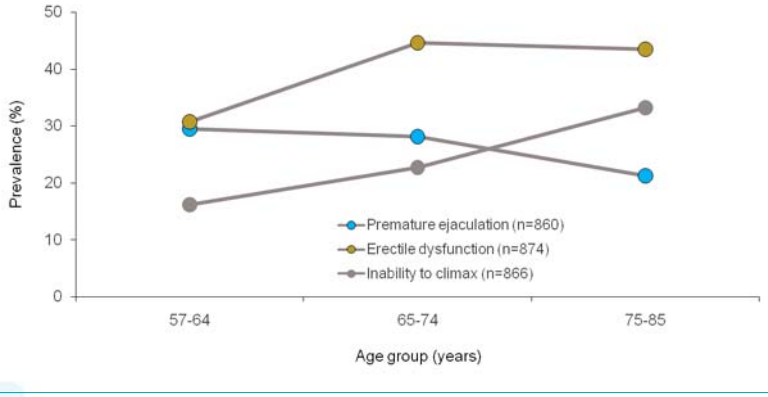


PE defined as 'climaxing too early'
ED defined as 'trouble achieving or maintaining erection'

Laumann et al. (1999) JAMA 281:537-544

勃起障礙的盛行率會隨著年齡增加

National Health and Social Life Survey analysis



PE defined as 'climaxing too quicky'
ED defined as 'difficulty achieving or maintaining erection'

Lindau et al. (2007) NEJM 357:762-774

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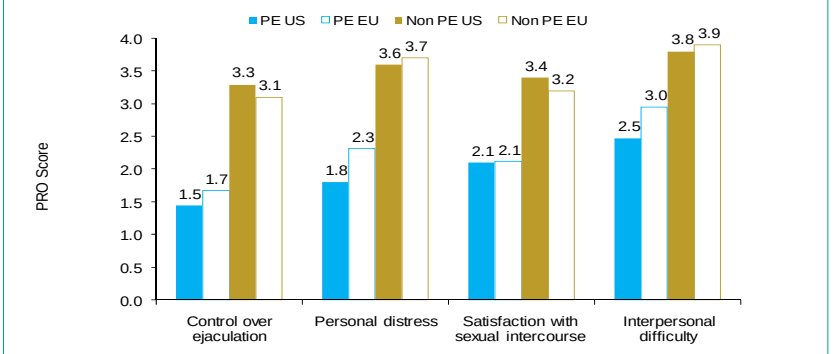
EU和US,伴侶有早洩以及伴侶沒有早洩的病患自我評估結果(PRO)比較

早洩的負擔: 所有早洩患者的病患自我評估結果(PRO)分數都比較差



Study codes: R096769-PRE-3004 (EU); C-004-2004 (US);
*Scores: second visit; higher scores indicate *better* functioning for all measures

Patrick et al (2005) J Sex Med. 2: 358-367; Giuliano et al (2008) Eur Urology 53: 1048-1057

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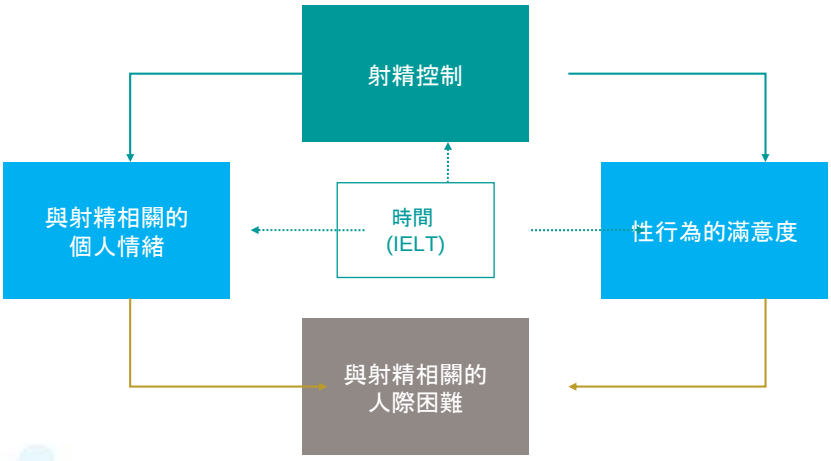
早洩中控制是關鍵



Adapted from Patrick et al. (2007) J Sex Med 4(3):780–788

Hypothesis for PE in the central nervous system

- PE maybe a result of a low ejaculatory threshold caused by either low 5-HT and/or abnormal (diminished) sensitivity of the postsynaptic 5-HT2C receptor.
- Pharmaceuticals that increase serotonergic activation of the postsynaptic 5-HT2C receptor, including clomipramine and the selective serotonin reuptake inhibitors, move the set point to a higher threshold, delaying ejaculation.

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Different definition of PE

- AUA update
- ICD-10
- DSM-IV-TR
- DSM-V

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Definition of PE in AUA update (2007)

- There is no global consensus of a definition of PE.
- The lack of control of ejaculation and inability to maintain intercourse long enough to sexually satisfy one self or one's partner's needs, or resulting in personal distress experienced by either partner are common criteria for the diagnosis of premature ejaculation

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Definition of PE in DSM-IV-TR

- "persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it".
- This definition of PE requires that the condition "must also cause marked distress or interpersonal difficulty", and states that it "is not due exclusively to the direct effects of a substance".

ICD-10 Definition of PE

- The inability to delay ejaculation sufficiently to enjoy lovemaking, which is manifested by either an occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required: before or within 15 seconds of the beginning of intercourse) or ejaculation occurs in the absence of sufficient erection to make intercourse possible”

The major difference between the abovementioned 2 definitions

- ICD-10 uses a cutoff point for the ejaculation time of 15 seconds, but does not provide literature on which this quantification is based.
- *DSM-IV-TR*, PE needs to cause marked distress and/or interpersonal difficulty before it can be classified as the sexual disorder PE.

Definition of PE in DSM-V

" ejaculation occurring within approximately 1 minute of vaginal penetration on 75% of occasions for at least 6 months ".

J Sex Med 2010;7: 672-689

Three main qualifications in definition of PE

- Short time interval between penetration and ejaculation.
- Lack of control over ejaculation.
- Distress by on or both partners.

早洩的特色

- 早洩為常見的男性性功能障礙，可見於各不同年齡層和國家
- ISSM 對早洩的定義為：
  - 射精總是或幾乎都發生於進入陰道後約 1 分鐘之內；以及
  - 陰道進入後幾乎沒有能力延遲射精；以及
  - 造成個人負面影響，例如困擾、煩惱、挫折及／或逃避性行為

Laumann et al.(1999) JAMA ; 281:537-544; Nicolosi et al.(2004) Urol 64(5):991-997; Porst et al.(2007) Eur Urology 51(3):816-23; McMahon et al (2008) J Sex Med 5:1590–1606

Intravaginal ejaculatory latency time (IELT)

- In 1994, Waldinger and colleagues
- the time from vaginal penetration to the start of intravaginal ejaculation-as an objective outcome measure.
- a median of 5.4 min.
- The 0.5 percentile equates to an IELT of 0.9 min
- The 2.5 percentile an IELT of 1.3 min .
- It is generally accepted but not included in most guidelines that men with an IELT of less than 1 minute have "definitive" PE.

Classification of Premature Ejaculation

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I. Partner satisfaction

- **Masters and Johnson: a man's inability to delay ejaculation long enough for his partner to reach orgasm in half of the attempts at intercourse.**
- **< 50 %**

II. Duration of intercourse

- 20 min --Kinsey et al
- 4-7 min ---1000 couples (1966)
- 10 min ---US couples
- 5 min---50% east German couples

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III. No. of thrusts and voluntary control

- 8 or 15 thrusts

IV. DSM-IV classification (Diagnostic and Statistical Manual)

- **Persistent or recurrent onset of orgasm and ejaculation with minimal sexual stimulation before, upon, or shortly after penetration and before the person wishes it.**
- **Marked distress or interpersonal difficulty.**

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- **Premature Ejaculation is defined as an intravaginal ejaculation latency time <1 min in > 90% of episodes of sexual intercourse, independence of age and duration of relationship.**

(Int J Psych Clin Pract 1998; 2: 287-93)

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V. Organic vs Psychogenic origin

- Psychological basis
- Penile hypersensitivity
- Neurobiological basis: serotonergic neurotransmission, disturbance of 5-HT2c or 5- HT1a
- Normal biological variability

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VI. Primary vs Secondary PE

- Primary : lifelong, persistence since first sexual intercourse
- Secondary: developing in men with previously normal ejaculation

Diagnosis

EUROPEAN UROLOGY 57 (2010) 804–814

Table 5 – Recommendations for diagnosis of premature ejaculation (PE)

Recommendations	LE	GR
Diagnosis and classification of PE is based on medical and sexual history. It should be multidimensional and should assess IELT, perceived control, distress, and interpersonal difficulty due to the ejaculatory dysfunction.	1a	A
Clinical use of self-estimated IELT is adequate. Stopwatch-measured IELT is necessary in clinical trials.	2a	B
Patient-reported outcomes have the potential to identify men with PE. Further research is needed before patient-reported outcomes can be recommended for clinical use.	3	C
Physical examination may be necessary in initial assessment of PE to identify underlying medical conditions associated with PE or other sexual dysfunctions, particularly ED.	3	C
Routine laboratory or neurophysiologic tests are not recommended. Additional tests should be directed by specific findings from history or physical examination.	3	C

ED = erectile dysfunction; LE = level of evidence; GR = grade of recommendation; IELT = intravaginal ejaculatory latency time.

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Treatment

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I. Psychological Therapy

Behavioral-Relationship Theories

- Masters and Johnson: PE is the result of conditioning or learning experiences in situations promoting short ejaculatory latency.

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- **Personal problems:**
  1st contact with prostitute, lack of intimacy, sexual guilt, shame, restrictive religious beliefs, anxiety, personal hypersensitivity
- Relationship problems:
  poor communication, conflict, mistrust, unrealistic beliefs about sex
- Female problems--dyspareunia

Stop-Start Technique
Squeeze Technique

- 當男性感到快要射精時, 先休息幾分鐘讓要射精的感覺過去, 然後再繼續進一步的性行為; 這是所謂的停止開始技巧. 另外也可以在快要射精時, 由男性或性伴侶輕壓陰莖龜頭的地方20秒, 之後停止刺激30秒, 然後再繼續性行為. 如此經過幾週的實戰經驗之後, 許多夫妻報告他們的問題有了改善, 當然這至少有部份是因為他們對自己的身體認識更多, 以及溝通的層次更進步了.

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- 教男性如何對抗逐漸增加的刺激, 經過幾週之後, 夫妻們學到沒有生殖器碰觸的樂趣和馬殺雞的技巧, 逐漸地建立到接觸生殖器, 最後才進行性交. 這跟把感覺去除不同, 常被稱為感覺集中技巧, 這對大部份類型的早洩有相當幫助, 但需長期治療才有效.

II. α-adrenoceptor blocker

- Phenoxybenzamine
- Old man

III. Dopamine antagonists

- Haloperidol ↔ Apomorphine
- Sulpiride (D2 antagonist)
- Vasotocin (oxytocin antagonist)
- Chlopromazine, Thioridazine (adrenergic receptor blocker)

IV. Antidepressants

- SSRI: Fluoxetine, Sertraline and Paroxetine --blocking serotonin reuptake, anticholinergic effect
- Clomipramine: blocking serotonin reuptake, sedative, anticholinergic and antihistame properties. (25-50 mg, 6 hours before)

V. Anxiolytics

- Benzodiazepine: 10% effect

VI. Topical Anesthetics

- Prilocaine-lidocaine cream: 2.5 g, 30 min before intercourse ↔ 82% effective rate

VII. Miscellaneous Agents

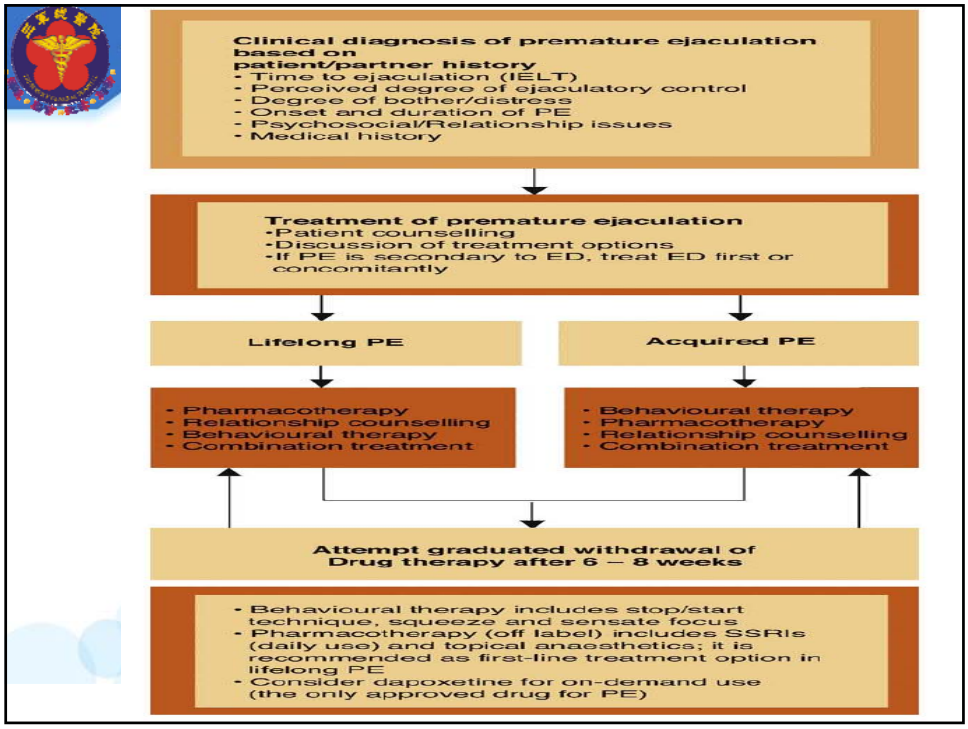
- Intracavernosal injection
- SS-cream: 106 P't prolong latency time > 2 min (82.2%, 10.3% with placebo)
- Neurectomy (80% were severed)
- Phosphodiesterase 5 inhibitors

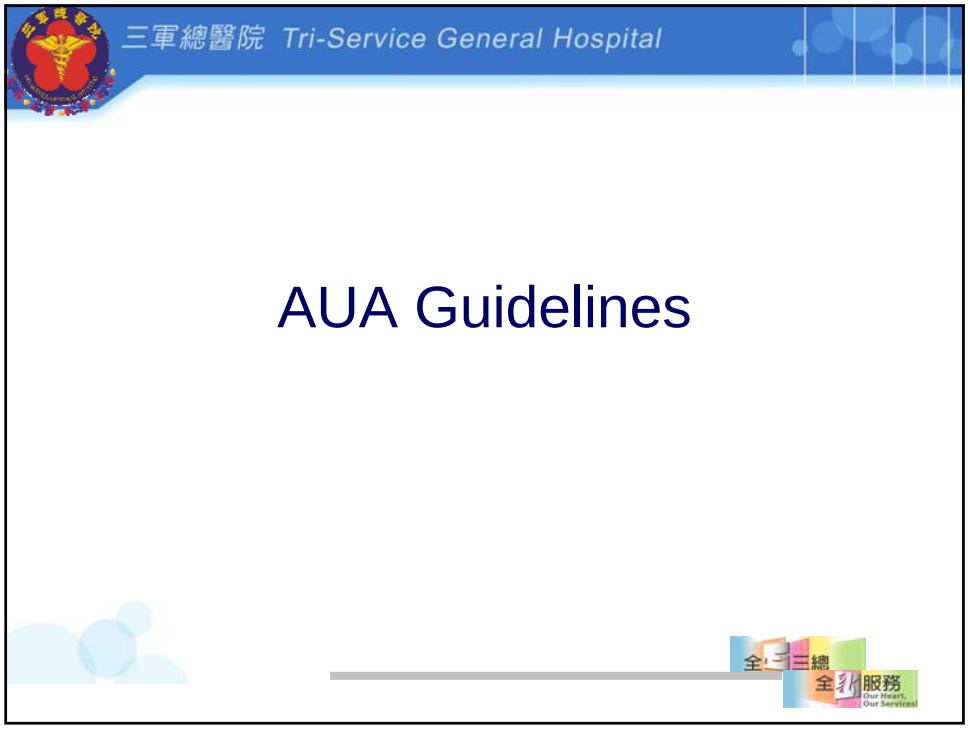
EAU Guidelines

Table 6 - Recommendations for premature ejaculation (PE) treatment

Recommendations	LE	GR
ED, other sexual dysfunction, or genitourinary infection (eg, prostatitis) should be treated first.	2a	B
Behavioural techniques can benefit PE; however, they are time intensive, require the support of a partner, and can be difficult to do.	3	C
Pharmacotherapy is the basis of treatment in lifelong PE	1a	A
Daily SSRIs are first-line, off-label, pharmacologic treatment for PE. The pharmacokinetic profiles of currently available SSRIs are not amenable to on-demand dosing.	1a	A
Dapoxetine is a short-acting SSRI that has been approved in Europe for the on-demand treatment of PE.	1a	A
Topical anaesthetic agents provide viable alternatives to SSRIs (off label).	1b	A
Recurrence is likely after treatment cessation.	1b	A
Behavioural therapy may augment pharmacotherapy to enhance prevention of relapse.	3	C

LE = level of evidence; GR = grade of recommendation; ED = erectile dysfunction; SSRIs = selective serotonin reuptake inhibitors.


Clinical diagnosis of premature ejaculation based on patient/partner history
- Time to ejaculation (IELT)
- Perceived degree of ejaculatory control
- Degree of bother/distress
- Onset and duration of PE
- Psychosocial/Relationship issues
- Medical history
Treatment of premature ejaculation
•Patient counselling
•Discussion of treatment options
•If PE is secondary to ED, treat ED first or concomitantly
Lifelong PE
Acquired PE
- Pharmacotherapy
- Relationship counselling
- Behavioural therapy
- Combination treatment
- Behavioural therapy
- Pharmacotherapy
- Relationship counselling
- Combination treatment
Attempt graduated withdrawal of Drug therapy after 6 – 8 weeks
- Behavioural therapy includes stop/start technique, squeeze and sensate focus
- Pharmacotherapy (off label) includes SSRIs (daily use) and topical anaesthetics; it is recommended as first-line treatment option in lifelong PE
- Consider dapoxetine for on-demand use (the only approved drug for PE)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AUA Guidelines

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AUA Guideline on Pharmacologic Management of Premature Ejaculation (1)

- The diagnosis of PE is based on sexual history alone. A detailed sexual history should be obtained from all patients with ejaculatory complaints.
- In patients with concomitant PE and ED, the ED should be treated first.
- The risk and benefits of all treatment options should be discussed with the patient prior to any intervention. Patient and partner satisfaction is the primary target outcome for the treatment of PE.

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AUA Guideline on the Pharmacologic Management of Premature Ejaculation (2)

- Premature ejaculation can be treated effectively with several serotonin reuptake inhibitors or with topical anesthetics. The optimal treatment choice should be based on both physician judgment and patient preference.

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Medical Therapy Options For The Treatment of Premature Ejaculation

- Nonselective serotonin reuptake inhibitor:
  Clomipramine (Anafranil) 25-50 mg/day or 25 mg 4-24 hrs pre-intercourse.
- Selective serotonin reuptake inhibitors (SSRIs):

  Fluoxetine (Prozac) 5-20 mg/day

  Paroxetin (Paxil) 10,20,40 mg/day or 20 mg 3-4 hrs pre-intercourse

  Sertraline (Zoloft) 25-100 mg/day or 50 mg 4-8 hrs pre-intercourse

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Medical Therapy Options For The Treatment Of Premature Ejaculation

- Topical therapies: Lidocaine/prilocaine cream (EMLA cream) 20-30 mins pre-intercourse

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Introduction of dapoxetine

- SSRI with a rapid onset and short half-life.
- believed to potentiate serotonin levels across the CNS by inhibiting neuronal reuptake. (Giuliano, 2006)
- Experimental evidence indicates that ejaculation is inhibited by serotonin throughout the descending pathway of the brain.


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Crile Building A
Cole Eye Institute
Walker Center
Visitor Parking 2
THE CLEVELAND CLINIC

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感謝聆聽

端午佳節快樂

敬請指教及提問

CNS Control of Ejaculation

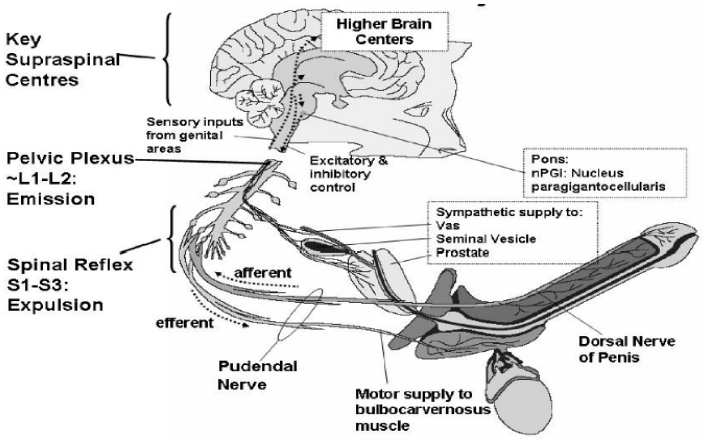
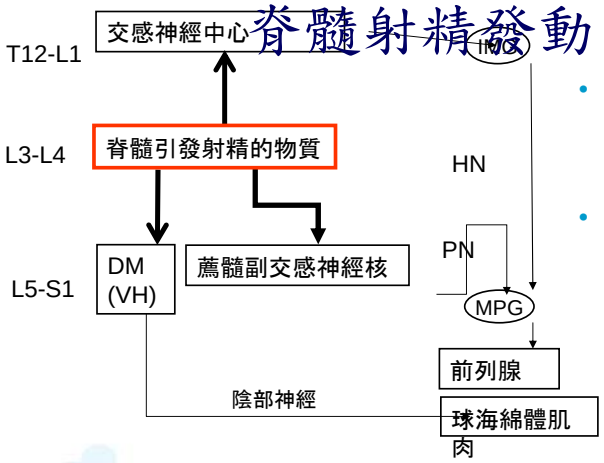


FIG. 2. Ejaculatory pathway

腰脊髓丘腦神經細胞協調射精 — 脊髓射精發動器



- 大鼠體內 L3–L4 級之 LSt 神經細胞，連結至前列腺和 BS 肌肉
- LSt 神經細胞負責調節和協調射精時的遺精和排出階段

Xu et al (2006) Neuroscience 138(2):561-573

BS：球海綿體；DM：背內側核；HN：下腹神經；
IMG：腸系膜間神經節；L：腰部脊神經；LSt：腰脊髓丘腦；MPG：主要骨盆神經節；
PN：骨盆神經；T：胸部脊神經；VH：腹側角

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Neurotransmitters

- Under strict control by multiple neurotransmitters.
- Most of our knowledge is based on a rat model
- Serotonin,5 hydroxytryptamine (5-HT) and dopamine have a predominant role over cholinergic, adrenergic, oxytocinergic and GABA nergicneurons.