CHAPTER 13

Committee 9 A

Disorders of Orgasm and Ejaculation in Men

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Disorders of Orgasm and Ejaculation in Men

C. G. McMahon, C. Abdo, L. Incrocci, M. Perelman, D. Rowland, B. Stuckey, M. Waldinger, Z. Cheng Xin

INTRODUCTION

Ejaculatory dysfunction or male orgasmic disorder (MOD) is one of the most common male sexual disorders. The spectrum of MOD extends from early ejaculation, through delayed ejaculation to a complete inability to ejaculate, anejaculation, and includes retrograde ejaculation. The sexual response cycle can usefully be conceptualized as having four interactive, non-linear stages: desire, arousal, orgasm, and resolution. The sexual dysfunctions are disruptions of any of these phases [1]. The fourth stage of orgasm is usually coincident with ejaculation, but represents a distinct cortical event, experienced phenomena logically both cognitively and emotionally. This four-stage model is consistent with the overall paradigm shift within urology, where both organic and psychogenic factors are recognized and integrated into our understanding of sexual function and dysfunction. Conceptualizing four stages provides a better heuristic platform for understanding ejaculatory dysfunctions as secondary to disruptions of any stage in the ejaculatory process, leading to appropriate and specific treatments [2].

THE EjACULATORY RESPONSE

Orgasm and ejaculation constitute the final phase of the sexual response cycle. Ejaculation is a reflex comprising sensory receptors and areas, afferent pathways, cerebral sensory areas, cerebral motor centres, spinal motor centres and efferent pathways. The ejaculatory reflex is predominantly controlled by a complex interplay between central serotonergic and dopaminergic neurons with secondary involvement of cholinergic, adrenergic, oxytocinergic and GABAergic neurons.

A. PHYSIOLOGY OF EjACULATION

There are 3 basic mechanisms involved in normal ante-grade ejaculation - emission, ejection and orgasm (Table 1) [3]. Ejaculatory dysfunction can result from disruption at any point in this cascade of events. Emission is the result of a sympathetic spinal cord reflex initiated by genital and/or cerebral erotic stimuli. Emission involves the sequential contraction of accessory sexual organs and the sensation of emission is due to distension of the posterior urethra. There is considerable voluntary control of emission. As the sensation of ejaculatory inevitability increases, voluntary control progressively decreases until a point at which ejaculation cannot be stopped is reached. Ejection also involves a sympathetic spinal cord reflex upon which there is limited voluntary control. Ejection involves bladder neck closure to prevent retrograde flow, rhythmic contractions of bulbocavernous, bulbospongious and other pelvic floor muscles, and relaxation of the external urinary sphincter. Intermittent contraction of the urethral sphincter prevents retrograde flow into the proximal urethra [4]. Orgasm is the result of cerebral processing of pudendal nerve sensory stimuli resulting from increased pressure in the posterior urethra, sensory stimuli arising from the verumontanum and contraction of the urethral bulb and accessory sexual organs.

The ejaculate can be divided into several fractions by serial biochemical analysis [5]. It comprises secretions from the seminal vesicles, prostate and bulbourethral (Cowper’s) glands, and spermatozoa. It is produced when the combining the secretions of the prostate and the contents of the ampullary parts of
the vasa deferentia, are washed out by fluid from the seminal vesicles and expelled from the urethra [6]. The spermatozoa are stored in the tails of the epididymes and the vas deferens ampullae. Approximately 50 - 80% of the entire ejaculatory volume is contributed by the seminal vesicles, 15-30% by the prostate gland and a small contribution is derived from the bulbo-urethral (Cowper’s) glands which is rich in enzymes and plasminogen activator [7]. Sper- 
matozoa normally constitute less than 0.1 % of the ejaculatory volume. The first fraction of the ejaculate contains the maximum number of spermatozoa, and subsequent fractions contain sequentially less.

Acid phosphatase, citric acid and zinc, emanating from the prostate, are also in highest concentration in the initial fractions of the ejaculate. Subsequent fractions contain fructose from the seminal vesicles, which increases in concentration towards the end of the ejaculatory process. The pH of the ejaculate increases in successive fractions as the acid component provided by the prostate is serially mixed with the more alkaline contribution of the fructose rich fluid from the seminal vesicles.

Table 1. The three stages of normal antegrade ejaculation

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<th>Emission</th>
<th>Sympathetic spinal cord reflex (T10–L2)</th>
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<td>Genital and/or cerebral erotic stimuli with considerable voluntary control</td>
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<td>Peristaltic contraction of epididymis and vas deferens</td>
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<th>Ejection</th>
<th>Parasympathetic spinal cord reflex (S2–S4)</th>
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<td>Limited voluntary control</td>
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<tr>
<td>Rhythmic contractions of bulbocavernous/pelvic floor muscles</td>
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<td>Bladder neck closure</td>
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<td>Relaxation of external urinary sphincter</td>
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<th>Orgasm</th>
<th>Build-up and release of pressure in posterior urethra</th>
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<td>Smooth muscle contraction of accessory sexual organs and urethral bulb</td>
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The ejaculatory reflex comprises sensory receptors and areas, afferent pathways, cerebral sensory areas, cerebral motor centres, spinal motor centres and efferent pathways (Figure 1) [8].

1. SENSORY RECEPTORS AND AREAS

The mucosa of the glans penis contains specialised sensory receptors, Krause-Finger corpuscles. They discharge along afferent nerves to the spinal cord and brain when repetitive and cumulative stimulation applied to the glans penis exceeds the excitation threshold. Sensory information from the penile shaft, perineum, testes and from variable extra-genital erogen organs e.g. nipples, anal sphincter, modulates, usually enhancing, afferent information from the Krause-Finger corpuscles.

2. AFFERENT PATHWAYS

Sensory information from the glans penis travels in afferent pathways to the spinal cord. Sensory fibres of the pudendal nerve, contained within the dorsal nerve of penis extend to the S4 level and autonomic fibres within the hypogastric plexus transmit information to the sympathetic ganglia located along the spinal cord.

3. CEREBRAL CONTROL OF EJACULATION AND ORGASM

Seminal emission and ejaculation are controlled by the paraventricular nucleus of the anterior hypothalamus (PVN) and the medial preoptic area (MPOA) (Figure 2) [9]. The medial pre-optic area (MPOA) is located rostral to the anterior hypothalamus and appears to have a pivotal role in augmenting copulatory behaviour. Electrical stimulation of the MPOA can elicit seminal emission or ejaculation in monkeys and rats [10, 11]. Electrical stimulation of the MPOA, also elicits the urethrogenital reflex in rats, which may mimic orgasm in humans [12]. This occurs in the absence of genital stimulation. This reflex is usually elicited in anesthetized, spinally transected rats by distending the urethra with saline and then suddenly releasing the pressure. This results in rhythmic firing of the hypogastric, pelvic, and motor pudendal nerves and rhythmic contractions of the perineal muscles, similar to those seen during orgasm in humans.
Figure 1: Nerves involved with emission and ejection. Sympathetic nerves from T10-L2 innervate the vas deferens, prostate and bladder neck, and contraction results in emission and bladder neck closure. Somatic nerve fibers in the pudendal nerve arise from S2-S4 and innervate the pelvic floor musculature, the contraction of which causes forceful ejection.

Figure 2: The ejaculatory reflex comprises sensory receptors and areas, afferent pathways, cerebral sensory areas, cerebral motor centres, spinal motor centres and efferent pathways.
Microinjection of moderate doses of a mixed D1/D2 dopamine agonist (apomorphine) or of a pure D1 agonist (thienopyridene), into the MPOA, promotes erections and copulation of male rats, apparently by increasing parasympathetic tone [13,14]. Higher doses of a mixed D1/D2 agonist, or of a selective D2 agonist, favour seminal emission and ejaculation [12]. Reduced libido during the ejaculatory refractory period may result from decreased dopamine release in the nucleus accumbens, a major terminal of the mesolimbic dopamine tract [15]. Dopamine is released in the MPOA of male rats in the presence of an estrous female, and increases more during copulation [16]. The levels of extracellular dopamine in the MPOA may regulate the phases of copulation, with high levels triggering ejaculation.

In a series of elegant rat experiments involving selective pharmacologic and/or radiofrequency lesions, Liu et al. demonstrated that the parvocellular neurons of the hypothalamic paraventricular nucleus (PVN) mediates erectile function in rats, whereas the magnocellular PVN neurons mediate ejaculation [17]. Oxytocinergic PVN neurons possibly modulate the male sexual response as evidenced by increased cerebrospinal fluid concentrations of oxytocin after ejaculation, augmented male sexual behaviour following intraventricular administration of oxytocin and decreased seminal emission in rats with lesions of the parvocellular PVN neurons [18].

The MPOA is also of importance to the cholinergic influence on sexual behaviour. Injections of the cholinergic agonists oxotremorine and carbachol cause a stimulation of sexual behaviour in male rats seen as a reduced number of intromissions preceding ejaculation, whereas injection of scopolamine reduces the number of animals intromitting and ejaculating [19].

The paragigantocellular (nPGi) reticular nucleus in the ventral medulla is a supraspinal locus of descending inhibitory influence on spinal nuclei mediating ejaculatory reflexes in the male rat [20]. Approximately 78% of the descending neurons from nPGi are serotonergic [21]. Lesions of the nPGi facilitate both the elicitation of the urethrogenital reflex and reflexive penile erections [22]. Selective serotonin neurotoxin lesions of the nPGi or transection of the spinal cord released the urethrogenital reflex from this tonic inhibition allowing the reflex to be elicited by urethral distension. However, stimulation of the MPOA can elicit the reflex, even if the nPGi and spinal cord are intact, suggesting that the MPOA may inhibit the nPGi, as well as stimulating an excitatory site.

4. **Spinal motor centers**

A spinal centre, located at the Th12-L1-L2 spinal level, is controlled by the sympathetic nervous system and is responsible for emission. A second centre, is located at the S2-S4 level, is controlled by the somatic nervous system and is responsible for expulsion.

5. **Eff erent pathways**

Emission is controlled by the sympathetic nervous system. The cell bodies of the sympathetic neurons are located in the lateral columns of the gray matter in the thoracolumbar segments of the spinal cord. Efferent sympathetic nerves emerge from the ventral roots of the spinal column at Th12-L2 to reach the sympathetic chains bilaterally (Figure 3).

The nerves proceed via the thoracic sympathetic chain to the caudal (inferior) enteric plexus, the major/minor splanchnic nerves, the celic/cranial mesenteric plexuses, and the intermesenteric nerves. Descending nerves from these ganglia encircle the aorta on each side before joining in the midline to form the hypogastric plexus just below the bifurcation of the aorta. The nerves proceed via the lumbar sympathetic chain and the lumbar splanchnic nerves to the caudal mesenteric plexus. The intermesenteric nerves and all lumbar splanchnic nerves merge into the inferior mesenteric and superior hypogastric plexuses. The former plexus mainly innervates the colon via the colonic nerve and from the latter arise paired hypogastric nerves. The junction of the hypogastric nerve and the pelvic nerve constitutes the pelvic plexus in the pelvis, which is an integration of sympathetic and parasympathetic nervous systems. The branches from this plexus innervate the epididymis, vas deferens, seminal vesicle, prostate, bladder neck and urethra (Figure 4) [23].

Norepinephrine is released from the axon terminal of the postganglionic neurons of the seminal tract in response to sympathetic signals passing through the hypogastric nerves. Norepinephrine activates smooth muscle 1-adrenergic receptors causing a rise in intracellular calcium, actin-myosin interaction, vas deferens smooth muscle contraction, a marked elevation of intraluminal pressure in the cauda epididymis/proximal vas, and propulsion of spermatozoa out to the ampulla. This ampullary wall distension and nerve signals trigger contraction of the ampulla to emit the content into the posterior urethra. Many substances including acetylcholine and neuropeptide-Y might modulate neurotransmitter release and/or
the resting tone of the smooth muscle of the vas deferens. Both nerve signal and distention of the wall of the ampulla might trigger contraction of the ampulla to emit the content into the posterior urethra.

Retrograde axonal tracing methods demonstrate that the majority of post-ganglionic neurons distributed in the vas deferens originate from the pelvic plexus [24]. The pelvic plexus receives neural input from both the hypogastric and pelvic nerves. Electrical stimulation of the hypogastric nerve elicited contraction of the vas deferens, while stimulation of the pelvic nerve caused no detectable motor responses [25-27]. Histochemical studies of the vas deferens have also shown that the adrenergic fibers mainly innervate the smooth muscle layers, whereas cholinergic fibers chiefly innervate the subepithelial layer [3].

Almost all the lumbar splanchnic nerves originate from L2 and/or L3 lumbar sympathetic ganglia (corresponding to L1-2 spinal levels) [23]. Preservation of the L2 and/or L3 lumbar splanchnic nerve in retroperitoneal lymph node dissection of testicular cancer allows preservation of ejaculatory function [28]. Partial interruption of the pathway from the spinal cord to the seminal tract would be expected to cause insufficient closure of bladder neck and retrograde ejaculation. Complete interruption of the pathway is likely to cause failure of emission.

The anatomical architecture of the peripheral sympathetic nervous system suggests probable cross-innervation and has been confirmed in the dog and rat [29]. Some signals in the lumbar splanchnic nerve cross to the other side of the body at the level of the caudal mesenteric plexus and/or the pelvic plexus. Preganglionic axons in the hypogastric nerve probably provide a bilateral innervation to postganglionic neurons in the pelvic plexuses, which also exhibit crossing to the bilateral vasa deferentia [29].

The pudendal nerve arises from the S2-4 segments of the sacral spinal cord and does not enter the pelvic plexus, but exits the pelvis through the greater sciatic foramen, re-enters it through the lesser sciatic foramen, and innervates the perineal striated muscles (Fig. 1). Rhythmic contractions of these perineal striated musculature including the bulbocavernosus and ischiocavernosus muscles, propels the seminal fluid. Sacral spinal cord injury patients usually show dribbling ejaculation due to the lack of contribution of the musculature.

Ejection is controlled by the parasympathetic nervous system. Efferent somatic fibres emerge from the anterior horn of the S2-S4 spinal segments
(Onuf’s nucleus), and travel in the motor branch of the pudendal nerve to innervate the pelvic floor striated muscles including the bulbospongiosus and bulbocavernosus muscles. Rhythmic contractions of the bulbocavernosus, ischiocavernosus and other pelvic floor striated muscles propel seminal fluid into the urethra. These muscles are innervated by the pudendal nerve and show excitement during ejaculation. Shafik measured the electromyographic (EMG) response of the bulbocavernosus, ischiocavernosus muscles and the external urethral sphincter during ejaculation induced by glans penis vibration and demonstrated that the ejaculatory mechanism consists of two distinct reflexes. Shafik reported increased electrical activity of the pelvic floor muscles and external anal (EAS) and urethral sphincters (EUS) during electroejaculation [31]. He suggested that the increased puborectalis muscle activity might express the prostatic secretions into the posterior urethra, that levator ani contraction elevates the prostate and partially straightens the prostatic-membranous urethral kink that might occur during erection and that the EAS and EUS contractions are believed to abort the urge to defecate or urinate and prevent leak of faeces, flatus, or urine during coitus. The rhythmic EUS contraction at ejaculation might act as a «suction ejection pump,» sucking the genital fluid into the posterior urethra while being relaxed and ejecting it into the bulbous urethra upon contraction.

The marked elevation of blood pressure, tachycardia, tachypnoea and perspiration that accompanies ejaculation are probably elicited by catecholamines secreted from the adrenal medulla. The adrenal medulla receives sympathetic nerves via the thoracic sympathetic chain and the major/minor splanchnic nerves.

II. NEUROCHEMICAL CONTROL OF EJACULATION

Dopamine and serotonin are important neurotransmitters in the brain. Many studies have been conducted to investigate the role of the brain in the development and mediation of sexuality, and dopamine and serotonin have been identified as essential neurochemical factors.

1. DOPAMINERGIC CONTROL

It has been known for a long time that treatment with dopaminergic drugs has a significant effect on the sexual behaviour of rodents. Kimura et al. attributed the dopaminergic system, particularly in the anterior hypothalamus, with a sexual facilitatory role [32]. Gessa & Tagliamonte proposed the «dopamine positive-serotonin negative» hypothesis [33]. However, dopamine-serotonin balance is more complex as evidenced by the paradoxical hypersexuality of spontaneous involuntary orgasm reported with some members of the selective serotonin re-uptake inhibitor (SSRI) class of anti-depressant drugs.

Five types of dopaminergic receptors have been identified. On a pharmacological basis, these subtypes have been divided into two families: the D1- and D2- family. The D2 family has the most important therapeutic role and the D1-family might have an important modulating effect on the D2-receptors. A possible sexual response regulatory role of dopamine is suggested by the observation that dopamine is released in the MPOA of male rats in the presence of an oestrous female, and progressively increases during copulation eventually triggering ejaculation [15]. In addition, electrical stimulation of the MPOA, even in the absence of genital stimulation, also elicits the urethrogenital reflex in rats, resulting in sequential firing of the hypogastric, pelvic, and motor pudendal nerves and rhythmic contractions of the perineal muscles, similar to those seen during orgasm in humans.

2. SEROTONERGIC CONTROL

Whereas dopamine, via D2 receptors, promotes seminal emission/ejaculation, serotonin is inhibitory. A potent vasoconstrictor, subsequently identified as serotonin, was first identified in the blood more than 100 years ago. An endogenous factor, enteramine was found in the enterochromaffin cells of the gut by Erspamer in 1940 [34]. This factor was subsequently structurally identified as 5-hydroxytryptamine (5-HT), found to be identical to the serum vasoconstrictor and called serotonin [35, 36].

Eighty percent of the total body serotonin is found in the enterochromaffin cells in the gastrointestinal tract [37]. Peripheral 5-hydroxytryptamine acts as a vasoconstrictor, platelet aggregator when released from platelets, a neurotransmitter in the enteric plexuses of the gut and as an autocrine hormone when secreted by the enterochromaffin cells in the gastrointestinal tract, pancreas and elsewhere [38]. Circulating 5-HT is unable to enter the brain as it cannot cross the blood-brain barrier.

The serotonergic system of the brain was initially localised in the 1960s using Falck-Hillarp histoche-
mical techniques. More recently, the development of antibodies against 5-HT and autoradiographic techniques have permitted identification of detailed 5-HT receptor locations [39]. In 1979, Peroutka and Snyder first identified different 5-HT receptors using radioligand binding technology. Currently, at least 16 different receptors have been characterised, e.g. 5-HT1a, 5-HT1b, 5-HT2a, 5-HT2b, etc [40]. Although the function and localization of many of these receptors is becoming increasingly clear, much remains unknown.

Serotonergic neurons are widely distributed in brain and spinal cord and are predominantly found in the brainstem, raphe nuclei and the reticular formation. There are two different groups of serotonergic neurons. A rostral group with cell bodies located in the midbrain and rostral pons project their axons into the forebrain. A second caudal group of serotonergic neurons with cell bodies in medulla project their axons into spinal cord [124]. The rostral part of the 5-HT system comprises the caudal linear nucleus, the dorsal and median raphe nuclei and the reticular formation of the pons and midbrain. The caudal system contains the nuclei raphe magnus, pallidus and obscurus, the adjacent reticular formation, solitary nucleus and the nucleus subcoeruleus [41].

The ascending projections from the rostral 5-HT neurons comprises two parallel but functionally and morphologically distinct pathways [41]. Projections that arise from the median raphe nucleus and are called the «basket-axon» system, comprise thick fibres (M-fibres) that branch into short, thin fibres and form multiple, large, round boutons (varicosities) and extensive synapses. The second system arises from the dorsal raphe nucleus and has thin fibres (D-fibres) which branch extensively and are characterised by multiple fusiform-like boutons (varicosities) which do not seem to contain any synaptic structures. Both systems are extensively distributed throughout the brain. In the cerebral cortex, both M- and D-fibres co-exist whereas the striatum receives only fine D-fibres and the gyrus dentatus primarily receives the thick M-fibres. The caudal raphe nuclei project to the caudal brain stem and spinal cord. The raphe magnus nucleus predominantly projects to the dorsal horn of the spinal cord. The nuclei pallidus and obscurus project to the ventral horn, intermediate zone and the intermediolateral cell column of the thoracolumbar and sacral spinal cord. Most of the afferent projections to the caudal raphe nuclei arise from the mesencephalic periaqueductal grey area and the medial cell groups of the hypothalamus and pre-optic area, the so called «limbic system» [42].

Serotonergic neurons use a variety of different mechanisms to self-regulate their own activity. Synaptic cleft 5-HT and 5-HT neurotransmission are regulated by somatodendritic 5-HT1A autoreceptors, presynaptic 5-HT1B autoreceptors and a 5-HT transporters re-uptake system (Figure 5). Each of these mechanisms is a negative feedback system which reduces synaptic cleft 5-HT and prevents over-stimulation of the postsynaptic receptors. Somatodendritic 5-HT1A autoreceptors are found in high concentrations on the cell bodies and dendrites of serotonergic neurons in raphe nuclei. They are activated by endogenous 5-HT and cause a reduction in firing rate of 5-HT neuron and reduced 5-HT neurotransmission. This endogenous 5-HT probably originates from somatodendritic release as opposed from synaptic release. Administration of the selective 5-HT1A receptor agonist, 8-OH-DPAT, to rats lowers central 5-HT levels and causes male rats to ejaculate at the first or second intromission. Activation of 5-HT1A receptors is attenuated or blocked by activation of 5-HT2C receptors. Presynaptic 5-HT1B autoreceptors also inhibit 5-HT release into synaptic cleft. This receptor is linked to an inhibitory (G protein) transaction mechanism which blocks the release of 5-HT and blocks the release of 5-HT from axonal vesicles, the exact mechanism of which has yet to be identified.

Large numbers of 5-HT transporters (5-HTT) are located predominantly on axonal terminals but also

![Figure 5](image-url): Synaptic cleft 5-HT and 5-HT neurotransmission are regulated by somatodendritic 5-HT1A autoreceptors, presynaptic 5-HT1B autoreceptors and a 5-HT transporters re-uptake system.
on the serotonergic cell bodies and its dendrites and glial cells. As 5-HT is released into the synaptic cleft from pre-synaptic axonal vesicles, 5-HT transporters re-uptake and remove 5-HT from the synaptic cleft, preventing over-stimulation of the postsynaptic receptors. After blockage of 5-HT transporters by selective serotonin re-uptake inhibitor class drugs (SSRIs), synaptic cleft 5-HT increases but is counteracted by activation of 5-HT1A autoreceptors which inhibit further 5-HT release.

The cerebral serotonergic (5-HT) system exerts an inhibitory role on ejaculation and male sexual activity in the rat model. Serotonin is released in the anterior lateral hypothalamus (LHA) of male rats at the time of ejaculation [43]. In 1969, Tagliomonte and Gessa reported that the serotonin depletor, P-chlorophenylamine (PCPA) promoted aggression, insomnia and aberrant, often compulsive hypersexual behavior in rats suggesting that the cerebral serotoninergic (5-HT) system exerts an inhibitory role on male sexual activity in the rat model [44]. Micro injection of a selective serotonin reuptake inhibitor (SSRI) into the LHA delayed both the onset of copulation and also delayed ejaculation after copulation had begun [43]. This parallels the reported adverse effects of the SSRI class of antidepressant drugs, which include decreased libido and delayed ejaculation/orgasm. Kondo and Yamanouch localised this inhibitory action to serotonergic neurons in the median raphe nucleus [45]. Lorrain et al. suggested that the observed increase in extracellular 5-HT in both the anterior lateral hypothalamus and MPOA of male rats following ejaculation, may inhibit subsequent ejaculation and is responsible for the ejaculatory refractory period [43]. The post ejaculatory decrease in libido may result in part from decreased dopamine release in the nucleus accumbens, a major terminal of the mesolimbic dopamine tract [16]. Dopamine in the nucleus accumbens has been related to motivation and/or reward related to numerous behaviors, including eating, drinking, copulation, and drug addiction. Therefore, one site at which SSRI drugs may inhibit both libido and ejaculation is the LHA. While the nucleus accumbens probably mediates the SSRI-induced decrease in libido, it probably does not influence ejaculation directly. The structure mediating that effect is not known; however, neurons from the LHA do descend to the lumbar spinal cord, where the neurons controlling genital reflexes reside.

Different 5-HT receptor subtypes may have opposing effects on sexual function. In 1981, Ahlenius reported that activation of 5-HT1A receptors in male rats with a selective agonist shortens the ejaculatory latency time [46]. Hillegaart et al. recently confirmed this but also reported that activation of 5-HT1B receptors inhibited male rat ejaculatory behaviour [47]. Berendsen demonstrated that activation of 5-HT1A receptors is attenuated or blocked by activation of 5-HT2C receptors [48]. More recently, Rehman et al. suggested that 5-HT1A receptors at different locations (brain, raphe nuclei, spinal cord and autonomic ganglia) may modulate rat sexual behaviour in opposing ways [49].

3. GABAergic Control

Several studies have identified an inhibitory and regulatory role in sexual functioning in rats of gamma-aminobutyric acid (GABA). Administration of GABA or compounds that induce elevated levels of GABA in the cerebrospinal fluid inhibits sexual behaviour. Elevated CSF GABA levels have been demonstrated during the post ejaculatory interval in male rats and during weaning in female rats also suggesting an inhibitory role. Benzodizepines, used in the treatment of anxiety, are believed to exert their effect through enhancement of GABAergic neurotransmission. Diazepam inhibits sexual behaviour in male rats, suggesting a possible mechanism for anxiety induced psychogenic sexual dysfunction [19].

It is estimated that 30-40% of neurons in the CNS use GABA as their primary neurotransmitter. GABA-receptors are divided into two classes on a pharmacological basis: GABA<sub>A</sub> and GABA<sub>B</sub>. GABA-receptors are distributed throughout the CNS, and it is estimated that 30-40% of neurons in the CNS use GABA as their primary neurotransmitter. GABA<sub>A</sub> receptors are probably tonically (and constantly) activated, while GABA<sub>B</sub> receptors are activated only under certain physiological situations. Activation of a GABA receptor has an inhibitory effect on the target neuron, such that a higher concentration of other neurotransmitters (eg. dopamine, serotonin) is required to achieve a neurotransmission of the same intensity.

GABA<sub>A</sub> agonists inhibitory sexual behaviour as evidence by a reduced number of mounts and intromissions when these drugs are administered systemically or locally in to the medial pre-optic area [50]. GABA<sub>A</sub> antagonists, on the contrary, have no effect on sexual behaviour when administered systemically but when administered by micro-injection direct in to the medial pre-optic area have a positive sexual
effect and reduce the ejaculatory latency time (as above). Male rats that are non-copulators also achieve benefit from GABA antagonists. The GABA\textsuperscript{B} receptor subtype also have an important role in mediating GABA’s inhibition of sexual behaviour. Systemic injection of the GABA\textsuperscript{B} agonist, baclofen results in a decrease in the number of rat mounts, intromissions and erections [50,51].

4. CHOLINERGIC CONTROL

Cholinergic receptors are divided into two classes: muscarinic and nicotinic receptors. Although both are found in almost all parts of the human body, the nicotinic receptor is seen in particularly high concentrations at the neuromuscular junction, autonomic ganglia and in the brain. Through its effect on cognition and blood flow via its action on the cholinergic system of the forebrain, nicotine regulates and/or coordinates a large array of central nervous system functions.

Administration of nicotinic receptor agonists such as nicotine or carbachol or physostigmine, anti-cholinesterase inhibitor, potentiate cholinergic neurotransmission and results in a reduction of sexual behaviour in rats. Low doses of nicotine have been reported to cause elevated levels of serotonin in the brain. As previously described, enhanced serotonergic neurotransmission most often results in an inhibition of sexual behaviour. Cholinergic antagonists such as atropine or scopolamine, exert an inhibitory effect on sexual behaviour. Micro-injection of scopolamine into the ventricles of the brain, prolongs initiation of copulation and reduces the number of intromissions and ejaculation in rats [50]. Micro-injection of the cholinergic agonists oxotremorine or carbachol into the MPOA causes a stimulation of sexual behaviour in male seen as reduced ejaculatory latency time.

5. ADRENERGIC CONTROL

The wide distribution of adrenergic receptors throughout the peripheral and central nervous system makes the adrenergic nervous system an essential part of the mechanism that controls many different physiological functions including sexual function. In the CNS, alpha-adrenergic receptors are present throughout the brain, while beta-1 and -2 receptors are found only in the cortex and cerebellum. Although noradrenaline effects both erection and ejaculation, it is difficult to conclude whether peripheral or central neurotransmission is essential in determining the direction of the effect. It is reasonable to conclude that a cholinergic-adrenergic balance is essential to keeping sexual functions in balance. As such priapism has been reported as an adverse effect of alpha-adrenergic blockade with the alpha-1 antagonists prazosin especially if cholinergic activity is reduced or eliminated at the same time [51]. Prazosin has also been shown to increase the ejaculatory latency time and the post ejaculatory interval in both rats and humans.

6. NITRIC OXIDE

Nitric oxide (NO) is becoming recognized as one of the important intracellular messengers in the brain [52,53]. Several authors have reported that NO might be involved in the regulation of emotional and behaviour [54-56]. There is a possibility that brain NO is involved in regulating male rat sexual behaviour. Mellis reported the role of NO in a specific brain area on male copulatory behaviour, especially penile erection [57, 58]. Sato et al. investigated the influence of the extracellular nitric oxide (NO) level on male rat copulatory behavior [59]. Micro-injection of the NO precursor, L-arginine into the MPOA, induced significant elevations of extracellular NO and a increased male copulatory behaviour with significant increase in mount rates. Microinjection of the NO synthase inhibitor N-monomethyl-L-arginine (L-NMMA) significantly reduced NO levels and inhibited copulatory behaviour. These findings suggested that the elevation of extracellular NO in the MPOA facilitates male copulatory behaviour of rats, whereas the decrease of NO reduces their copulatory behaviour.

There is a possibility that NO facilitates male copulatory behaviour through acceleration of dopamine release. Lorrain and Hull reported that micro-injection of the NO precursor, L-arginine, into the MPOA increased the extracellular dopamine level [60]. Moreover, they showed the possible role of CGMP/NO pathway in the control of dopamine release during copulation [61]. They suggested that NO may play a role in control of male copulatory behaviour and temperature regulation through the modulation of monoamine release. L-Glutamate elicits an intracavernous pressure increase in the MPOA [62]. It increases NO production by activation of NMDA receptors. This suggest that NO in the MPOA directly promotes penile erection, and supports a biological role of NO in the MPOA for positive mediation of male sexual behaviour.

Hull et al. demonstrated that microinjection of the
NO synthase inhibitor, N-nitro-L-arginine methyl ester (NAME) decreased the number of erections, but also increased the number of seminal emissions and decreased the latency to the first seminal emission [63]. The results indicate that not only does nitric oxide promotes erection in intact male rats, but may also inhibit seminal emission, probably by decreasing sympathetic nervous system activity. Kriegsfeld reported that mice homozygous for eNOS gene deletion have striking ejaculatory anomalies [64]. A significantly higher percentage of eNOS gene deletion mice than normal controls ejaculated during the testing period, requiring less stimulation and few mounts and intromissions.

Intraperitoneal injection of pilocarpine caused a dose-related seminal emission adult male rats [65]. The seminal emission response to pilocarpine was greatly reduced in atropinized animals, suggesting a cholinergic effect. N-nitro-L-arginine methyl ester (NAME), a nitric oxide synthesis inhibitor, inhibited the pilocarpine-induced seminal emission, which was reversed by L-arginine or by coinjection of sodium nitroprusside. These results suggest that nitric oxide mediates the inhibitory neurotransmission responsible for seminal emission in pilocarpine stimulated rats.

Consistent with this, Ferrari et al. have demonstrated that the specific type V isoenzyme phosphodiesterase inhibitor, sildenafil, modifies central DA-mediated behaviour in rats [66]. They also reported that sildenafil diminished both the ejaculation latency and the inter-intromission interval in normal rats [67]. Following castration, the effect of sildenafil on copulatory function was not observed but as restored following testosterone replacement.

It is also known that testosterone is fundamental for a normal mating pattern, which is totally disrupted by castration and can be restored by the replacement of the hormone. It has been suggested that testosterone-induced activation is linked to increased synthesis and/or release of DA in the brain and NO could be the bridge between testosterone and DA for copulatory behaviour [68].

### B. THE EFFECTS OF DRUGS ON ORGASM AND EJACULATION

**I. ANIMAL STUDIES**

Male rat studies (Table 2) have demonstrated that serotonin (5-hydroxytryptamine: 5-HT) and 5-HT receptors are involved in the ejaculatory process. As far as is currently known, 5-HT2C and 5-HT1A receptors determine the speed of ejaculation. For example, studies with d-lysergic acid diethylamide and quipazine, which are nonselective 5-HT2C agonists, suggest that stimulating 5-HT2C receptors delays ejaculation [255].

However, 2,5-dimethoxy-4-iodophenyl-2-aminopropane, which equally stimulates 5-HT2A and 5-HT2C receptors, also increases ejaculation latency [256], whereas the selective 5-HT2A receptor agonist 2,5-dimethoxy-4-methylamphetamine does not have this effect [255]. On the other hand, activation of postsynaptic 5-HT1A receptors by the selective 5-HT1A receptor agonist 8-hydroxy-2-(di-n-propylaminotetralin) in male rats resulted in shorter ejaculation latency [255].

Administration of selective serotonin reuptake inhibitors (SSRIs), results in higher levels of 5-HT in the synapse due to active blockade of 5-HT transporters in the presynaptic membrane [124]. Initially, the 5-HT level is only mildly increased, but due to desensitisation of the 5-HT1A and 5-HT1B/1D autoreceptors, 5-HT levels in the synaps increase highly. The higher levels of 5-HT consequently activate the postsynaptic 5-HT2C and 5-HT1A receptors [124,257]. Acute administration of clomipramine and SSRIs does not lead to a significant change in sexual behavior of male rats [258]. However, chronic administration with fluoxetine [259] and paroxetine [260] significantly delays ejaculation latency time in male rats. Chronic administration of fluvoxamine however exerts only a mild change in male rat sexual behavior.
Based on 5-HT2C and 5-HT1A receptor interaction data in animals Waldinger et al. [124, 126, 261] formulated the hypothesis that in men with early ejaculation there is a hyposensitivity of the 5-HT2C and/or hypersensitivity of the 5-HT1A receptor. The hypothesis that activation of postsynaptic 5-HT receptors delays ejaculation is supported by numerous studies in humans with different SSRIs. However, in these studies it is not obvious whether similar receptor subtypes, that is 5-HT2C and 5-HT1A receptors, are also involved in human ejaculation since SSRI treatment activates many different postsynaptic subtype receptors. To find an answer 2 human studies with the 5-HT2C blocking antidepressants nefazodone [181] and mirtazapine [182] were performed. In a double-blind placebo controlled study with the 5-HT2C/5-HT2A receptor antagonist and 5-HT/noradrenaline reuptake inhibitor nefazodone, 400 mg nefazodone daily did not exert any ejaculation delay in contrast to a significant delay after 20 mg paroxetine daily and 50 mg sertraline daily. In a similar study the 5-HT2C/5-HT3 receptor antagonist, and noradrenergic and specific serotonergic antidepressant mirtazapine did not induce ejaculation delay compared with the significant delay after 20 mg paroxetine daily and 50 mg sertraline daily. In a similar study the 5-HT2C/5-HT3 receptor antagonist, and noradrenergic and specific serotonergic antidepressant mirtazapine did not induce ejaculation delay compared with the significant delay resulting from 20 mg paroxetine daily. In both studies nefazodone and mirtazapine did not delay ejaculation. Further studies with selective 5-HT2C and 5-HT1A agonist and antagonists are encouraged to elucidate still undiscovered pharmacological mechanisms underlying the ejaculatory process.

### III. SIDE EFFECTS OF SPECIFIC DRUGS ON EJACULATION

#### 1. DOPAMINE

The centrally acting neurotransmitter dopamine is known for its involvement in control of male rat sexual behavior. Taking the parameters of mount and intromission frequencies and latency to ejaculation as measures of copulatory activity, most reports indicate that dopamine has a stimulatory effect on ejaculation that is exerted via D2 receptors. Enhancement of the ejaculatory behavior and the decrease in intromission frequency stimulated some authors to call this altered behaviour a rat model for «early ejaculation». Some dopamine (DA) receptor agonists, such as apomorphine, N-n-propyl-norapomorphine, lisuride and 3-[(3-hydroxyphenyl)-N-n-propyl-piperidine (3-PPP) may cause ejaculation in male rats with receptive females sooner and after fewer penile intromissions than controls. The doses of DA agonists needed to produce “early ejaculation” on male rats are within the low dose range needed to stimulate DA autoreceptors. In this manner, it is suggested that this phenomenon in rats results from inhibition of DA neurotransmission [262].

#### 2. MORPHINE

Several studies have shown that systemic and central administration of morphine inhibits male rat sexual behavior. It is suggested that the inhibitory effects of morphine may be mediated by the kappa receptor [263]. However, in one study, a small proportion of male rats reacted differently on a low dose of systemic morphine: there was a decrease of ejaculation latency, and in the number of intromissions prior to...
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<tr>
<th>DRUG CLASS</th>
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<th>MECHANISM OF ACTION</th>
<th>EFFECT ON EJACULATION/ORGASM</th>
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<td>Decrease Latency</td>
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<td>Morphine</td>
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<td>Pipothiazine</td>
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### Table 3. Effects of drugs on ejaculation (CTD)

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<td>Amphetamines</td>
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Table 3. Effects of drugs on ejaculation (CTD)

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<td>Cocaine</td>
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<td>Heroin</td>
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<td>Marijuana</td>
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<td>Methadone</td>
<td>μ Agonistic activity (inhibition of activity in locus coeruleus – nucleus related with anxiety and fear)</td>
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<tr>
<td></td>
<td>Tobacco</td>
<td>Activity in cholinergic and noradrenergic transmission</td>
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ejaculation [263]. In another recent study, morphine had marginal effects on sexual motivation in general, but reduced ambulatory activity in male rats. In this study, neither dopamine nor opioids seem to be important for sexual incentive motivation [264]. These conflicting results indicate that at least there is a role for the enkephalines in the modulation of sexual behavior in the male rat.

3. ECSTASY

The amphetamine analog MDMA, better known as the recreational drug ecstasy, is known and feared for its neurotoxic properties. It reduces brain concentrations of serotonin by inhibition of the metabolism and by long-lasting degeneration of 5-HT nerve terminals, as well as by decreasing the number of 5-HT uptake sites. In an experiment with male rats, Dornan and collaborators found that a chronic administration of MDMA, caused less rats to display mounting behavior, and an increase in ejaculation latency in the responders [265]. These results are conflicting with the above-described studies with serotonin receptor agonists and antagonists, because a decrease in central 5-HT would cause an increase in male rats’ sexual behaviors. Probably, since MDMA has such dramatic effects in the brain, other factors may have played an important role in this experiment.

4. GABA

The neurotransmitter gamma-aminobutyric acid (GABA) occurs in the brain tissue. Two distinct types of GABA receptors are recognized: GABA_A and GABA_B. There is some evidence that the GABAB receptor agonists (like baclofen) inhibit sexual behavior in male rats, independently from the effects on motor systems. But in other study, baclofen was ineffective in reduce sexual behavior in male rats while muscimol (a GABA_A receptor agonist) when given into the paraventricular nucleus of the hypothalamus reduce dose-dependently male rats sexual behavior [266].

5. YOHIMBINE

The alpha2-adrenoceptor blocking agent yohimbine has been known for its aphrodisiac properties in rats and humans. In male rat studies, it increased mounting behavior without the need for physiological levels of serum testosterone. When looking at the effects on ejaculation, a decrease in ejaculation latency, intercopulatory interval, and post-ejaculatory interval is found. Others alpha2-adrenoceptor antagonists, such Rauwolscine and Idazoxan also have stimulatory effects on ejaculatory function in animal models [267].

6. MONOAMINE OXIDASE INHIBITORS

The monoamine oxidase inhibitors (MAOIs) are mainly used in the treatment of neurotic or atypical depression. These drugs increase the levels of epinephrine, norepinephrine, dopamine and serotonin. The MAOIs have been known for their sexual side effects, with an incidence up to 20-40%. Delayed or inhibited ejaculation is reported for isocarbazid, phenelzine and tranylcypromine.

7. CYPROHEPTADINE

Cyproheptadine is an antihistaminic, formerly used in Cushing’s disease and anorexia nervosa. It also increases serotonin levels in the brain. Several reports indicate that cyproheptadine is able to convert drug-induced orgasmic failure in both men and women.

8. BENZODIAZEPINES

A number of benzodiazepines effective in treating generalized anxiety and panic attacks are also known to inhibit ejaculation in some men, presumably by enhancing gamma-aminobutyric acid (GABA). These drugs include diazepam, lorazepam, lorometazepam, temazepam, flunitrazepam, flurazepam, nitrazepam, chloridiazepoxide, and alprazolam. However the effect on ejaculation is not so intensive as that other psychotropics such SSRIs. Less than 10% of men experience an inhibition of ejaculation with these anxiolitic drugs [268].

9. STIMULANTS

Amphetamine is a stimulating drug with affinity for different receptors in the central nervous system. It stimulates release of dopamine, inhibits monoamine oxidase and blocks the reuptake of both catecholamines and serotonin. In male rats, methamphetamine inhibits the intromitting and ejaculating behavior [269]. It is reported to delay ejaculation in subjects without ejaculatory dysfunction. Cocaine is an addictive «recreational» drug and stimulates the central nervous system through blocking of monoamine transporters. Different reports confirm that delayed ejaculation appears to be the most common sexual side effect.

10. Dopamine antagonists

Dopamine antagonists block central dopamine receptors and clinically used as antipsychotics or neuroleptics. Ejaculation may be prevented by centrally acting
dopamine receptor blockers such as pimozide, sulpiride and haloperidol [262,270]. Thioridazine, chlorpromazine delay ejaculation but also block adrenergic receptors [271]. Atypical neuroleptics such as risperidone and clozapine, that block dopamine and serotonin receptors, have been reported to delay ejaculation.

11. ALPHA 1-BLOCKING AGENTS

Potent alpha-adrenergic blocker agents such as phenoxybenzamine hydrochloride, alphuzosine and terazosine suppress ejaculation by inhibition of the sympathetic nervous activation of the ejaculatory reflex [272-274].

12. NITRIC OXIDE DONORS

NO-donors such as sodium nitroprusside, S-nitroso-glutathione, S-nitroso-N-acetylcysteine, S-nitroso-N-acetylcysteine-ethylester and linsidomine have been demonstrated to reduce adrenergic tension in isolated human seminal vesicle strip preparations. A potential role of these agents in the treatment of early ejaculation exists [275].

13. ANTIDEPRESSANTS

Selective Serotonin Reuptake Inhibitors class antidepressants (SSRI) increase synaptic cleft 5-HT levels delay ejaculation probably by action on 5-HT2 and 5-HT3 receptors. The antidepressants nefazodone (5-HT2 antagonist) and mirtazapine (5-HT2 and 5-HT3 antagonist) antagonize these receptors and produce no clinically significant ejaculatory delay. Tri cyclic class antidepressants inhibit ejaculation in a dose dependent manner due to their anticholinergic and alpha-adrenergic antagonistic properties [89]. The influences of different drugs on ejaculation are delineated in Table 3.

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**C. PREMATURE EJACULATION (PE)**

1. DEFINING CRITERIA

Both DSM-IV-R and ICD-10 provide definitions of premature (early) ejaculation. Specifically, DSM-IV-R [69] defines premature (early) ejaculation as “the persistent or recurrent ejaculation with minimal stimulation before, on, or shortly after penetration and before the person wishes it. The clinician must take into account factors that affect duration of the excitement phase, such as age, novelty of the sexual partner or situation, and recent frequency of sexual activity. The disturbance causes marked distress or interpersonal difficulty. PE is not due exclusively to the direct effects of a substance (e.g., withdrawal from opioids).”

ICD-10 [70] indicates “the general criteria for sexual dysfunction must be met. There is an inability to delay ejaculation sufficiently to enjoy lovemaking, manifest as either of the following. 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); ejaculation occurs in the absence of sufficient erection to make intercourse possible. The problem is not the result of prolonged absence from sexual activity.” These two sources provide similar though not identical conceptual frameworks for classifying an individual as having PE. Included in both is reference to three general criteria: short ejaculatory latency, a lack of sexual satisfaction, and a lack of self-efficacy regarding the condition. This last component is noted as “ejaculation before the person wishes” in DSM IV-R, and the “inability to delay ejaculation sufficiently to enjoy lovemaking…” in ICD-10.

2. OPERATIONALIZING THE CRITERIA

Each of the three criteria above has been operationalized, although not always with consistency [71]. The first criterion—short ejaculatory latency—is typically operationalized by intravaginal ejaculatory latency time (IELT), defined by the number of seconds/minutes between vaginal intromission and
ejaculation, averaged over a number of attempts. ICD-10 indicates that latencies of 15 sec or less are consistent with a PE diagnosis. Other sources suggest latencies up to 60 sec—90% of ejaculations of men with this disorder occur within this timeframe [72] —or even up to two minutes [73] (Figure 6). IELT’s of 2 minutes or less show minor overlap with those of men without PE, which typically range from about 2 to 10 min. Accordingly, any latency under 2 min suggests a possible PE diagnosis.

Whether latencies should be exactly timed (e.g., using chronometers of some sort) or whether estimations by the man and/or his partner are sufficiently accurate to quantify this criterion is yet undecided. The former strategy offers greater precision and less bias [72], perhaps with the downside of being intrusive and/or overemphasizing the weight of objectively quantified measures relative to patient’s subjective assessment of the problem. Interestingly, recent data indicate that estimations of IELT tend to over- rather than under-estimate ejaculatory latencies, suggesting a bias toward “misses” rather than “false positives.” Whatever method is used, IELT should be considered only one of several conditions important for a PE diagnosis.

Mere temporal latency—that is, penile time spent intravaginally—does not capture a relevant defining characteristic of PE, namely “ejaculation with minimal stimulation” (DSM-IV-R). As a result, the “number of penile thrusts” to ejaculation probably represents a more valid assessment of the amount of penile stimulation. However, IELT is generally considered the more reliable measure and is, within the larger population of men, correlated with the number of penile thrusts [74].

The second criterion—self-efficacy or the patient’s ability to control the dysfunctional response—distinguishes men who ejaculate rapidly because they are incapable of any other response from those who do so for any number of other reasons, including ones related to the situation or the partner. In recent research, self-ratings of «control over ejaculation» have been used successfully as a self-efficacy measure that differentiates PE men from sexually functional men [75-77]. Men with PE rate their ejaculatory control around 2 to 4 (1 = not at all; 7 = complete control), whereas functional men typically rate their control at 4 or higher. Since actual control over the ejaculatory reflex is itself something of a matter of debate, measures of self-efficacy more relevant to assessing successful treatment of PE may include such items as the “ability to delay ejaculation” or to “the ability to overcome early ejaculation”.

The third criterion—concern or distress about the condition—is usually satisfied by the mere fact that the man (often with his partner) approaches the clinic seeking help for the sexual problem. In situations where participants are recruited into an experimental or clinical investigation, several questions might be included in a screening questionnaire that directly address the issue of concern or distress. Most commonly these items query the man (and when possible his partner) about his general level of sexual satisfaction, with further elaboration about anxiety or concern surrounding the sexual problem and about the quality of the sexual relationship. Standardized
measures of general anxiety (e.g., BSI [78]), sexual functioning (e.g., GRISS [79]) or dyadic distress (Dyadic Adjustment Scale [80]) might also be included to further assist in operationalizing this criterion.

• Exclusionary factors
Both DSM-IV and ICD-10 definitions prescribe conditions that exclude an individual from a PE diagnosis. These include early ejaculation mediated by alcohol, substance use, or medication; a context that leads to very high levels of arousal because of novelty of partner or situation; and a low frequency of sexual activity.

3. Diagnostic subgroups
Given the lack of consensus (and supporting data) regarding possible etiologies of PE, it is not surprising that identification of clear subtypes of PE based upon cause has not been successful. Nevertheless, classification of PE into various subtypes based on developmental histories and response characteristics has sometimes proved useful. For example, most clinicians and researchers distinguish between lifelong and acquired PE, and between PE that is limited to specific situations or partners and that which is more global. Knowing that the patient has had a lifelong history of PE not specific to one partner may argue toward a biological and/or cognitive etiology. As such, the need to address interpersonal and relationship issues may be less important in these men. In contrast, knowing that the PE developed recently in specific situations and in conjunction with erectile dysfunction may suggest the need to address relationship issues and attend less to a biological etiology.

a) Relevant covariate conditions of men with PE
Men with high risk for PE often report other symptoms that characterize their condition, and these might be used to assist in identifying individuals with PE, particularly when they are not familiar with the nosological terminology employed in clinical settings. Such men may present their problem using language that reflects various other aspects of their dysfunctional experiences.

b) Penile sensitivity
Many PE men report a high level of penile sensitivity, although empirical data supporting such hypersensitivity is mixed [81-83]. Perceived hypersensitivity may reflect strong responsivity or low thresholds of the ejaculatory reflex as much as hyperresponsivity of sensory receptors in the penis.

4. Ejaculatory latency during masturbation
PE is defined primarily by ejaculatory latency and control during coital activity. Nevertheless, many PE men report short latencies during masturbation as well. Others, on the other hand, experience short latencies during intercourse but not masturbation [73]. Presumably men in this latter category are better able to control the timing of ejaculation during masturbation because they are less aroused and/or can exert more control over the intensity of penile stimulation. Alternatively, the absence of anxiety that emanates from the evaluative nature of psychosocial interactions surrounding intercourse may diminish or eliminate the conditions typically leading to early ejaculation.

5. Desynchronization of arousal and ejaculation
Ejaculation and orgasm typically define the high point of arousal within the sexual response cycle. Yet some PE men characterize their ejaculation as being unexpected, that is, occurring prior to their anticipated peak of arousal. Furthermore, there is evidence from psychophysiological analysis suggesting that in response to psychosexual stimulation, PE men report lower sexual arousal but closer proximity to ejaculation when compared to sexually-functional counterparts [73]. PE men may underestimate their level of arousal, or alternatively, may reach orgasm at submaximal arousal levels and prior to their anticipated peak arousal.

6. Dissociation of semen expulsion and somatic contractions
Ejaculation involves the dual responses of sympathetically-controlled emission of semen mediated through prostate function and bladder neck closure and somatically-controlled expulsion of semen through rhythmic contractions of the bulbocavernosal and anal sphincter musculature. The former response, which is associated with ejaculatory inevitability, typically acts as the stimulus for the second reflex response, which is primarily associated with the experience of orgasm. A limited subset of PE men not only report short latencies to ejaculation, but also fail to experience the full complement of somatic contractions, with the resulting consequence of semen dribbling from the penis. Although this condition is sometimes associated with acetylcholine inhibitors, it has been know to occur in the absence of medications as well.
7. Co-existing Erectile Dysfunction

A significant number of men with PE also report having problems achieving and/or maintaining an erection, estimated as high as 30% [77]. Typically, these men ejaculate without a full erection, with penile tumescence reaching a maximum—although less than complete erection—at the moment of ejaculation. The extent to which these co-existing dysfunctions are either independent or interrelated is unknown, although careful analysis of the developmental histories of each problem may assist in devising an appropriate treatment strategy.

8. Frequency of Ejaculation

Self-reported frequency of ejaculation/orgasm has been related to short ejaculatory latencies, with PE men exhibiting lower frequencies of sexual activity and orgasm relative to sexually functional counterparts [84-86]. Both ICD-10 and DSM-IV-R exclude men from the diagnosis who ejaculate rapidly due to infrequent sexual activity. Presumably, lower frequencies in PE men lead to shorter IELT’s because arousal levels may be unusually high and the normal inhibition of ejaculation caused by the male refractory period plays a diminished role.

II. THE ETIOLOGY OF PREMATURE EJACULATION

Historically, attempts to explain the etiology of early ejaculation has included a diverse range of biogenic and psychological theories (Table 4). Most of these proposed aetiologies are not evidence based and are speculative at best. Psychological theories include the effect of early experience and sexual conditioning, anxiety, sexual technique, the frequency of sexual activity and psychodynamic explanations. Biogenic explanations include evolutionary theories, penile sensitivity, central neurotransmitter levels and receptor sensitivity, degree of arousability, the speed of the ejaculatory reflex and the level of sex hormones. The lack of an operationalized definition for PE and the presence of methodological problems related to the inadequate definitions used, is a common flaw in the majority of these studies.

1. Anxiety

Anxiety has been reported as a cause of PE by multiple authors and is entrenched in the folklore of sexual medicine as the most likely cause of PE despite scant empirical research evidence to support any causal role [86-90]. Several authors have suggested that anxiety activates the sympathetic nervous system and reduces the ejaculatory threshold as a result of an earlier emission phase of ejaculation [87, 89]. Strassberg et al. (1990) used a multivariate definition of PE incorporating both latency and control dimensions and failed to demonstrate any difference in sexual anxiety between a control group of men with normal ejaculatory control and men with PE [91]. Kockott reported that men with PE and low levels of sexual anxiety ejaculated rapidly during both intercourse and solitary masturbation [92]. Men with PE and high levels of sexual anxiety, however, ejaculated rapidly only during sexual intercourse and had superior ejaculatory control during solitary masturbation. This study contained several methodological flaws which make interpretation of results difficult. Anxiety was only measured during sexual intercourse and not during solitary masturbation and was subjectively self evaluated by the patient and not by an objective validated inventory. Furthermore, anxiety levels in a control group of men with normal ejaculatory control were not examined.

Isolated anecdotal reports suggest a potential role for anxiolytic medication in the treatment of PE. Segraves (1987) reported the successful treatment of a 71-year-old man with primary PE with the benzodiazepine, lorazepam whereas Cooper and Magnus (1984) failed to distinguish any difference in ejaculatory latency times of men with PE at baseline or following treatment with beta-blocking drug, propranolol or placebo [93, 94].

The possibility that high levels of anxiety and exces-
sive concerns about sexual performance and potential sexual failure might distract a man from monitoring his level of arousal and recognising the prodromal sensations that precede ejaculatory inevitability has been suggested as a possible cause of PE by several authors [88,90,95]. The causal link between anxiety and PE is speculative, is not supported by any empirical evidence and is in fact contrary to empirical evidence from other researchers. No difference in either subjectively or objectively measured sexual arousal or sexual sensory awareness was found between men with PE and men without PE in a laboratory setting [85,91,96]. In direct contradic-
tion to this theory, Kockott et al. found that men with severe PE demonstrated higher objective and subjective measures of arousal than men with erectile dys-
functions or normal control subjects [92, 97]. This study was limited, however, to solitary stimulation without ejaculation making extrapolation of results to ejaculation during sexual intercourse difficult. All published studies ignore the possibility that the presence of anxiety in men with PE may just as likely be the result of PE as the cause and fail to establish the direction of the presumed causal relationship.

2. EARLY SEXUAL EXPERIENCE
Masters and Johnson were the first of several researchers to suggest that early sexual experiences characterized by anxiety and rush, might condition men to develop a subsequent pattern of early ejaculation [86,98]. However, no empirical evidence was offered to support this hypothesis and no distinction was made between men with lifelong PE and men with acquired PE. All researchers failed to recognise that anxiety and rush define the early sexual experiences of most men. Furthermore, the early sexual histories of a control group of men with subsequent normal ejaculatory control were not examined to determine whether early conditioning experiences are unique to men with PE. Williams reported a small cases series of four men with acquired PE and suggested that some men might initially condition themselves to ejaculate quickly due to their perception that their partner was sexually disinterested, and remain subsequently unable to control ejaculation when the initial negative circumstances were no longer present [89]. The resultant sexual anxiety and concern about the legitimacy of the partner’s renewed sexual interest might serve to maintain the PE.

3. FREQUENCY OF SEXUAL INTERCOURSE
The evidence to support a link between ejaculatory control and frequency of sexual activity is conflicting. Speiss reported that the frequency of sexual activity in men with PE is lower than age-matched controls with normal ejaculatory control whereas Strassberg failed to demonstrate any relationship [85,96]. The mechanism of this relationship is yet to be characterised but may include reduced performance anxiety, a higher ejaculatory threshold or superior ejaculatory control due to earlier and superior recognition of prodromal ejaculatory sensations. Consistent with these observations, McMahon and Touma in a placebo controlled cross-over study of the efficacy of paroxetine in treating PE, reported that the pre-treatment frequency of sexual intercourse increased from 0.5 to 3.2 times per week with paroxetine but fell to pre-treatment levels with placebo [99]. The observation that men with PE may develop a pattern of sexual avoidance may also explain this reduced frequency of sexual intercourse indicating that the polarity of the relationship between PE and frequency of sexual activity remains undetermined [97].

4. EJACULATORY CONTROL TECHNIQUES
Zilbergeld suggested that some men with adequate ejaculatory control might consciously learn a variety of effective sexual techniques for deferring ejaculation during their early sexual experiences and unconsciously continue to use those techniques subsequently [88]. These techniques may include thought distraction, pelvic floor muscle contraction or alteration of the speed and /or depth of penile vaginal thrusting. Data to support this hypothesis is weak and studies to evaluate the use and effectiveness of control techniques in men with PE is lacking.

• Evolutionary
Hong suggested that PE was the result of evolutionary natural selection, arguing that rapid intercourse allowed insemination of more females with transmission of a possible genetic basis for PE to more offspring [100]. The observation that primate courtship and sexual contact are often extended is inconsistent with this hypothesis [101].

5. PSYCHODYNAMIC THEORIES
Abraham was the first to suggest a psychodynamic basis of PE. He theorised that PE was the adult manifestation of unresolved and excessive narcissism during infancy which resulted in exaggerated importance being placed on the penis and the associated pleasure of urination [102]. He offered no empirical
basis for this theory and subsequent studies by other authors have failed to demonstrate any evidence for his narcissism hypothesis [103]. Kaplan initially theorised but later recanted a link between male anger and hostility towards women and PE, suggesting that the man both symbolically «soils» the woman and denies her sexual pleasure as a result of an unconscious, deep-seated hatred of women [87, 95].

6. PENILE HYPERSENSITIVITY

Multiple authors have proposed that men with PE have hypersensitive penis’ and either reach ejaculatory threshold more rapidly or have a lower ejaculatory threshold than men with normal ejaculatory control [91,102-104]. A limitation of the universal applicability of this theory is its inability to explain acquired PE.

Xin et al. demonstrated that men with early ejaculation have lower biothesiometric vibration perception thresholds and significantly shorter mean somatosensory evoked potential latency times of the glans and penile shaft than controls [82, 105]. Paick et al. and Rowland, however, were unable to reproduce these findings, reporting no significant statistical differences between normal controls and patients with primary early ejaculation [81,106]. Several authors have reported that penile sensitivity reduces with ageing [104,107,108]. This is probably due to loss of the fastest conducting peripheral sensory axons from the third decade, dermal atrophy, myelin collagen infiltration and pacinian corpuscle degeneration [106]. Some researchers have suggested this observation as the reason why PE is reported more often in younger men [90]. However, a more attractive explanation of this observation is the presence of greater anxiety and less frequent sexual activity in the absence of a long-term relationship resulting in fewer sexual opportunities to learn ejaculatory control. Fanciullacci et al. measured significantly higher amplitude cortical somatosensory evoked potentials following penile electrical stimulation in men with severe lifelong PE compared to control subjects [109]. They hypothesized that men with PE have a greater representation of the penile sensory nerve supply in the cerebral cortex than controls, and suggested this as an indication of an organic basis for PE. Consistent with this is the report by Bradley that the cortical distribution of the dorsal nerve of the penis is larger in men with lifelong PE [110]. Brain imaging with functional MRI and positron emission tomography is required in humans to identify the central control of the ejaculatory process in man.

Research into the relationship between PE and penile hypersensitivity has effectively excluded the impact of other factors which may affect the level of arousal achieved and the time required to reach and the level of the ejaculatory threshold. These factors include the extent of use of fantasy and other forms of non-contact stimulation. If penile sensitivity were, in fact, a cause of PE, men with PE would be expected to ejaculate more quickly than controls only in situations where there was direct stimulation of the penis.

7. HYPER-EXCITABLE EJACULATORY REFLEX

Several authors have suggested that PE is due to a defective and early ejaculatory reflex with a faster emission and/or expulsion phase. Several authors have reported a link between PE and a malfunctioning bulbocavernosal reflex (BCR). The bulbocavernosus muscle (BCM) surrounds the urethral bulb and is one of several muscles responsible for the expulsive phase. This hypothesis lacks a firm physiological basis as the emission phase of the ejaculatory process has already started by the time the BCM contracts.

Gospodinoff (1989) suggested that a faster bulbocavernosus reflex (BCR) might impede the process of learning to control ejaculation [111]. One of the most common treatments for PE, the squeeze technique, is based on the assumption that PE is due to a defective ejaculatory reflex [112]. Colpi et al. demonstrated that men with lifelong PE, defined as ejaculating within 15 thrusts of penetration, have higher amplitude sacral evoked potentials measured through perineal and perineal surface electrodes compared to age-matched controls [113]. He concluded that men with PE have a hyper-excitatory BCR. However, the sacral evoked potential latency in men with lifelong PE did not differ from age-matched controls which is inconsistent with this conclusion. Similar results were reported by Fanciullacci et al [109]. A shorter BCR latency time in men with lifelong PE compared to men with acquired PE and normal controls was, however, reported by Gospodinoff [111]. Unlike Colpi et al., Gospodinoff’s study groups were not age matched and the cohort of men with acquired PE were 13 years younger than men with lifelong PE, suggesting that the difference in these two groups could be due to age-related degeneration of the afferent and efferent nerves of the BCR. In addition, men with acquired PE had a longer BCR latency time than controls which is at odds with the suggestion that PE is due to a hyper excitable ejaculatory reflex.
8. Arousalability

Laboratory studies using solitary stimulation during audiovisual stimulation have failed to demonstrate greater, more frequent or more rapid arousal in men with PE compared to a control group of sexually non-dysfunctional men [85].

9. Abnormal Levels of Sex Hormones

Although there are several reports of a possible link between PE and levels of sexual hormones, a careful review of the published literature fails to confirm any causal link. Pirke failed to demonstrate any difference in the levels of free and total testosterone and luteinizing hormone (LH) during serial sampling between men with PE, ED or normal controls [114]. Cohen, however, reported that levels of free and total testosterone, LH and Follicle Stimulating Hormone (FSH) were reduced in men with PE. He also reported that 4 of 12 men with PE had elevated prolactin levels and suggested that PE may be the result of a hypothalamic-pituitary disorder [115]. He subsequently reported that pharmacological treatment of PE with a selective serotonin reuptake inhibitor (SSRI) class drug improved ejaculatory latency and elevated androgen and LH levels [116].

10. Genetic Predisposition

A familial predisposition to early ejaculation was first reported by Schapiro in 1943 [103]. Waldinger reported that 10 of 14 first-degree male relatives of men with lifelong PE also suffered from PE with an IVELT of less than 1 minute [117]. Based on this small study, the odds ratio of a familial occurrence of PE far exceeds the incidence in the general community and supports Schapiro’s contention that PE may have a genetic basis.

11. 5-HT Receptor Sensitivity

The current understanding of the functional neuroanatomy and the role of central serotonin and dopamine neurotransmission in ejaculation are based on male rat studies. The hypothalamic medial preoptic area (MPOA) and the medullary nucleus paragiganto-cellularis (nPGI) in the ventral medulla have pivotal roles in the central control of ejaculation [118,119]. Electrical stimulation of or microinjection of dopamine agonists into the medial preoptic area promotes ejaculation [120]. It has been suggested descending serotonergic pathways from the nPGI to the lumbosacral motor nuclei tonically inhibit ejaculation and that disinhibition of the nucleus paragantocellularis results in ejaculation [20]. The prevalence of serotonergic neurons in the nPGI and the observation that selective serotonin re-uptake inhibitor class drugs inhibit ejaculation, suggests that the nPGI is a possible site of action of these drugs [22]. Coolen et al identified ejaculation initiated neural activation in several brain regions after ejaculation, including the posterodorsal medial amygdala, the posteromedial bed nucleus of the stria terminalis, and the medial parvicellular subparafascicular nucleus of the thalamus [121-123]. It is likely that afferent neurons ascend in the spinal cord to the medullary parvicellular subparafascicular nucleus and the other brain areas mentioned and activate ejaculation. These areas are extensively and reciprocally interconnected and probably form the basis of an ejaculation «brain circuit» [123].

Multiple dopamine and 5-HT receptor types have been identified. Studies using highly selective 5-HT receptor agonists and antagonists have identified a pivotal role of 5-HT2C and 5-HT1A receptors in the central control of ejaculation. Stimulation of the 5-HT2C receptors in male rats with non-selective 5-HT2C agonists such as d-lysergic acid diethylamide and quipazine, delays ejaculation [124]. Contrary to this, activation of postsynaptic 5-HT1A receptors by the selective 5-HT1A receptor agonist 8-hydroxy-2-(di-n-propylaminotetralin) in male rats facilitates ejaculation [125]. Waldinger et al hypothesised that lifelong early ejaculation in humans may be explained by either hypersensitivity of the 5-HT2C and/or hypersensitivity of the 5-HT1A receptor [124]. They suggested that men with low 5-HT neurotransmission and probable 5-HT2C receptor hypersensitivity may have their ejaculatory threshold genetically «set» at a lower point and ejaculate quickly and with minimal stimulation and often prior to reaching their erectile threshold. Men with a genetically determined higher set point men can sustain more prolonged and higher levels of sexual stimulation and can exert more control over ejaculation. Finally, men with a very high set point may experience delayed or absent ejaculation despite prolonged sexual stimulation and achieving a full erection [126]. Treatment with an SSRI class drug will activate the 5-HT2C receptor, adjust the ejaculatory threshold set point and delay ejaculation. The extent of ejaculatory delay may vary widely in different men according to the dosage and frequency of administration of SSRI and the genetically determined ejaculatory threshold set point. Cessation of treatment results in re-establishment of the previous set point within 5-7 days in men with
life long PE. Identification of the specific 5-HT receptor subtypes involved in early ejaculation is only possible by administering subtype selective 5-HT2C or 5-HT1A receptor ligands. Unfortunately these agents are not yet available for human use.

III. PSYCHOLOGICAL TREATMENT OF PREMATURE EJACULATION

1. THE RATIONALE FOR PSYCHOLOGICAL/BEHAVIORAL STRATEGIES

Even though a physiological basis for some types of PE has been suspected for years [130,131], until recently treatment options relied, quite understandably, mainly on behavioral and psychological procedures. First, psychological factors such as anxiety and negative affect have frequently been associated with sexual dysfunctions such as PE [1,132] and therefore treatment addressing such issues has represented a logically consistent approach. In contrast there had been little or no evidence pointing to a physiological mechanism that might underlie PE. Second, until the past five years, few tested and well-tolerated biologically based therapeutic procedures were available to clinicians for the treatment of PE. And third, the psychological-behavioral strategies for treating PE have been at least moderately successful in alleviating the dysfunction [133].

Although the new and often more expedient pharmacological therapies are overshadowing these traditional psychological-behavioral methods in the treatment of PE, the psychological-behavioral approach remains an attractive option for several reasons. The treatment is specific to the problem, is neither harmful nor painful, is less dependent on the man’s medical history, produces minimal or no adverse side effects, encourages open communication about sexuality in the couple which is likely to lead to a more satisfying sexual relationship [134,135], and has a permanence about it. Once the techniques have been learned and incorporated into lovemaking, PE men continue to have access to strategies that help them control their ejaculation. At the same time, there are drawbacks to the psychological-behavioral approach: it is time-consuming, often requires substantial resources of both time and money, lacks immediacy, requires the partner’s cooperation, and has mixed (and less well-documented) efficacy [136, 137].

2. EMPIRICALLY SUPPORTED PSYCHOLOGICAL APPROACHES

In addition to countering the current trend toward pharmacotherapeutic treatment for PE, clinical practitioners considering the use of behavioral and psychological strategies as part of their treatment protocol face particular difficulties. Strong pressure exists to provide a therapeutic treatment that falls within today’s cost containment managed care environment and that meets the criteria of being empirically validated or at least empirically supported. To be considered “empirically supported,” a therapeutic approach must be backed by (1) at least two studies showing it more effective than a waiting-list control group, or (2) at least two studies demonstrating effectiveness but which may have flawed sample heterogeneity, or (3) by a series of case studies in which the client sample was clearly specified and the treatment procedure described in a detailed manual.

Because of the tension between therapeutic and research objectives, it has been difficult to conduct carefully controlled, well-conceived studies that simultaneously provide needed treatment to clients whose lives are being adversely affected by their PE. As a result, there have been no treatment vs. matched-control tests of behavioral-psychological therapy on PE men, and relatively few self-as-control, waiting list, or even no-control studies [138]. More importantly, the lack of specific treatment protocols and of research funds to carry out well-designed studies to test those protocols has diminished the attractiveness of these approaches relative to evolving pharmacological strategies [139,140].

Two psychological-behavioral strategies enjoying substantial popularity among sex therapists have at least come close to meeting the criteria of empirically-supported. The first is the stop-squeeze method, developed by Semans [141] and later adopted by Masters & Johnson [86] in their sex therapy clinic. The second method, advocated by Kaplan [1], is the stop-pause method. Both methods suppress the urge to ejaculate by stopping sexual stimulation, but the former substitutes a squeeze of the glans penis for a pause in stimulation at the point of impending ejaculation.

• Details of successful psychological-behavioral methods of treatment for PE

The stop-squeeze method calls for the man to signal his partner as the ejaculatory urge builds. The couple then stops the sexual stimulation and the partner applies manual pressure to the glans of the penis until the urge is reduced, though not to the point where the erection is lost. Different amounts of time for the squeeze have been advocated, but there is no evidence to support any particular duration. Rather,
an individualistic approach that balances urge reduction while maintaining a moderate level of sexual arousal appears most effective [142]. With this strategy, the man must pay careful attention to his sexual sensations and stop activity well before ejaculatory inevitability. The stop-squeeze method is typically employed first with masturbation in a cycle of three pauses before proceeding to orgasm. Once successful, the method then progresses to a cycle of two pauses with intercourse in the female superior position, and finally to a cycle of two pauses with intercourse in the lateral position. This training requires an almost exclusive focus on the male’s experience of sexual stimulation and needs. While Masters and Johnson’s initial report of only a 2% short-term failure rate and 3% long-term failure for the stop-squeeze method revolutionized a field of PE treatment, subsequent studies have reported much lower success rates, in the neighborhood of 50-60% [143-145]. Long term success rates may be even lower. Undoubtedly, the success rates reported by Masters and Johnson were influenced by their carefully-selected clients, the intense format of their treatment, and the relatively high sexual naiveté of couples common during that era.

The start-stop behavioral approach to the treatment of PE men was developed by Kaplan [132] because it better simulated the final behaviors required to prolong ejaculation latency during intercourse. Weekly outpatient therapy resulted in a high success rate (80-90%) in men with primary, generalized PE (i.e., with all partners and often during masturbation). The combination of the stop-start method with marital therapy for couples who showed “resistance” (discussed below) during the treatment process was also quite successful in men with secondary early ejaculation [1,132]. Although Kaplan’s high success rates have been challenged, the differential procedures for patients with primary versus secondary appears to be a robust finding [145].

Detailed descriptions of both the stop-squeeze and start-stop behavioral methods have been provided in the literature [139, 142,144], with different therapists emphasizing their own variations. Some therapists advocate using techniques such as slowing down, breathing deeply, or moving [144] in a circular fashion, techniques that many men without PE develop without conscious awareness [144]. Others advocate adding a stage of ejaculatory control training with oral sex as an intermediate step between masturbation and coitus for couples who are comfortable with this particular activity [142]. Still others emphasize the importance of providing the couple with accurate information about the sexual response cycle and its physiological underpinnings [146,147]. Almost all agree that intercourse position is a relevant factor: the female superior and lateral positions allow for greater control than the male superior position [144,148].

3. PARAMETERS AFFECTING TREATMENT

The general procedures described above rather than any specific variations have received the strongest empirical support for effective treatment of PE. Furthermore, the purported lack of efficacy of various psychological/behavioral strategies may result less from the specific behavioral techniques associated with stop-squeeze/stop methods and more to a lack of attention to the parameters and context surrounding the treatment. In addition, long-term compliance is likely to be as much a mitigating factor for behavioral and psychological efficacy as it is with pharmacotherapeutic efficacy.

Three factors are important to successful outcomes when behavioral and psychological strategies are used. First, the man’s attention to and awareness of sexual and visceral sensations must be heightened. Second, the couple must de-emphasize the focus on coitus and develop a broader range of sexual expression. And third, the man, and to a lesser degree his partner, must develop alternative cognitive and behavioral strategies to enhance ejaculatory control. Beyond these specific techniques, the man’s motivation for treatment and openness to behavioral interventions and the partner’s positive assessment of the relationship are significant predictors of positive therapeutic outcomes.

Beyond these broad factors described above, other parameters appear to maximize treatment efficacy with psychological-behavioral strategies.

4. FREQUENCY AND INTENSITY OF TREATMENT

The two-week inpatient/intensive outpatient format originally described by Masters and Johnson offers advantages of great intensity and rapid change. Nevertheless, time, cost, and insurance factors make it unrealistic for most couples [142]. However, research does suggest that long intervals between sessions (bi-weekly or monthly) are insufficient during the early phase of therapy. The most effective treatment begins with 1-2 weekly sessions in order to provide adequate support for the change process, to
allow time for the couple to practice behavioral assignments at home, and to "unlearn" adjunctive behaviors (discussed below) that might exacerbate the dysfunction.

Because the long term benefits of psychological-behavioral treatment for PE often decline over time, treatment that lacks sufficient intensity or duration increases the likelihood of a "relapse," that is, a reappearance of early ejaculation symptomology [144]. In fact, such relapses are common in PE men. Yet, if the couple is not adequately prepared, the resulting setback can lead to sexual avoidance, the development of erectile dysfunction, and other adverse secondary effects. Strategies from the relapse prevention model [149], originally developed for the management of substance abuse, suggest that initial treatment intensity and duration should be designed to reduce the likelihood of relapse. For example, weekly treatment should continue until marked progress is made. Then, larger treatment intervals serve to maintain change and deal with difficulties that arise, with periodic sessions continuing six months after success is attained [144,146]. A further implication of the relapse prevention model is the need to plan for an appropriate response, should relapse occur. This includes decreasing the negativity associated with the setback by predicting its occurrence and assisting the couple in developing coping strategies to deal with the relapse. If follow-up appointments are yet continuing, the couple’s success in dealing with the relapse should be discussed in the session; if treatment has ended, the couple should be instructed to resume therapy if they are unable to cope with relapses.

5. TREATMENT FORMATS

A number of alternative formats for the treatment of PE have been investigated, including the use of bibliotherapy, group versus individual therapy, couples versus individual therapy, and marital versus sex therapy. Clinical research supports the use of bibliotherapy combined with some type of therapist contact for men having high motivation and relatively straightforward PE without co-morbid disorders [142]. However, PE men who have complicating factors such as individual or relationship difficulties (which includes the majority of sex therapy clients) or concomitant erectile problems benefit less from reliance on this format.

Data on group (vs. individual) treatment for early ejaculation are mixed. Some investigations have found the two formats equivalent whereas others have not [144]. Use of group therapy is primarily a matter of the couple’s preference and openness to receiving treatment in this structure. Some couples benefit from knowing their sexual problems are not unique and from hearing how other couples deal with them. A group format also provides an opportunity for men and women to meet with same-sex peers. On the other hand, most men find PE a highly sensitive issue (as is the couple’s overall sexuality) and are not comfortable discussing the topic in the presence of others. At present, the research literature cannot be used to defend either an exclusive use of a group format (which certain insurance plans might prefer) or an exclusive avoidance of group format (which some practitioners might prefer).

Treatment of PE in an individual format, however, is not as successful as working with couples. Individual treatment in the absence of a partner precludes the opportunity to practice behavioral and cognitive strategies in-situ. Still, instances arise when individuals are bothered by their PE and thus seek treatment without a partner. In such instances the stop-squeeze and stop-pause techniques may be adapted to masturbation, especially when intensity of arousal is enhanced by adding a lubricant and using erotic literature or fantasy [139]. This self-sexuality training can be complemented with education about the female and male sexual response cycles. Training of ejaculatory control through masturbation typically entails a goal of 15 minutes of sexual stimulation of varying intensity before reaching orgasm.

The relative importance of marital vs. sex therapy is an issue that has received some attention from researchers, but results are not sufficiently clear to yield specific answers. The question may be framed in the following way: Does marital therapy lead to enhanced sexual functioning or does sex therapy lead to enhance marital functioning. Generally, marital therapy prior to sex therapy for couples with significant relationship issues leads to better outcomes in sexual functioning, while marital therapy in non-distressed couples does not typically lead to improved sexual functioning. Conversely, sex therapy in non-distressed couples often does lead to improved marital functioning.

6. DEALING WITH RESISTANCE, INCLUDING PRIOR SELF-STRATEGIES

Some patients who seek counseling for PE exhibit various forms of “resistance” to the traditional behavioral approaches. Sources for this resistance include
situations where the dysfunction maintains a sexual equilibrium or hides the female partner’s sexual disorder or concerns; where the individual or couple has unrealistic expectations about sexual performance; where major relationship problems exist; where partner deceit is present; and where PE is the consequence of a major health problem [133]. Given the increasing attention to emerging pharmacological solutions for sexual problems, the refusal to reasonably explore cognitive/behavioral and relationship issues and the insistence on taking the “right pill” are becoming new sources of resistance.

Related to the concept of treatment resistance is the issue of “home remedies.” Prior to treatment, PE men may adopt coping strategies that actually worsen the condition [135], that is, the attempted solutions contribute to rather than ameliorate the problem [150]. For example, most PE men assume that paying less attention to the sexual stimuli through active distraction might help control their ejaculation. Yet this strategy counteracts the greater attention to sexual sensations needed to gain control over the timing of ejaculation. As a result, this remedy typically leads to an unsatisfying orgasm as well as PE, and may result in avoidance of sexual situations altogether. A second home remedy involves harder and faster thrusting by the man during his orgasm in an attempt to satisfy his partner. This strategy decreases the awareness of the sexual sensations of the ejaculatory response needed to gain greater control and reduces the enjoyment of the orgasm due to increased anxiety and focus on sexual performance. A third home remedy is for the man to apologize for the early ejaculation, an act that exacerbates existing feelings of anxiety and guilt, and is likely to lead to avoidance. Many couples report that an exclusive focus on the duration and quality of intercourse directly contradicts a healthy focus on developing a mutually satisfying sexual life. Indeed, a strong focus on coitus is counterproductive, particularly since many men without PE ejaculate within several minutes of intromission and a sizable percentage of women achieve orgasm through direct clitoral stimulation, not through intercourse [135].

Kaplan’s work of combining sex therapy with interpersonal approaches and accurate information about sexual functioning provides a model for working through these sources of resistance and challenging the negative coping strategies that might have developed in response to the dysfunction. At times, the “working through” process itself may result in progress even if the reason for the resistance is unclear. But for most couples, a careful preliminary assessment will help prepare the therapist for impediments to progress that can arise within treatment [1].

7. TREATING THE PERSON VS. TREATING THE PENIS

One of the great benefits of incorporating behavioral and/or psychological counseling into a treatment regime is that such approaches are more likely to address the psychoaffective and relationship concerns surrounding the dysfunctional response. The affective component of sexual response has long been theorized to play a role in causing or sustaining sexual dysfunction in men [91,132,151], with recent research verifying that compared with sexually functional men, men with PE exhibit higher negative and lower positive affect in response to erotic stimulation [152,153]. What has been unclear is whether the high negative and low positive affect in PE men is part of the original etiology or cause of the dysfunction, or whether it represents a reaction to failed genital response that then serves to exacerbate the problem.

Recent research actually supports both possibilities [154]. For example, positive emotions such as pleasant/enjoyable increase in PE men who respond to the ejaculatory-retarding effects of clomipramine treatment, but negative affects such as guilt/embarrassed and tense/worried do not show comparable decreases. In other words, pharmacotherapy appears effective in reinstating positive emotional responses to sexual stimuli in PE men, but negative emotions are not diminished, even when ejaculatory latencies are increased by as much as several minutes. Thus, even when pharmacological treatment is effective, further therapeutic strategies that emphasize open communication and relaxation with the partner to ease embarrassment and tension may further assist the client in overcoming negative dispositions associated with the dysfunction.

At a broader level, this study illustrates that the interpersonal dynamics that result from the dysfunction—including such factors as avoidance of intimacy on the part of the man and subsequent anger and distress on the part of the partner—may not always be reversed by a genital solution. In such situations, psychological and interpersonal issues may need to be addressed, at least if increased sexual satisfaction and an improved sexual relationship are viewed as important outcomes. Equally important is the recognition that because pharmacotherapy can alleviate a sexual dysfunction, the cause of their problem is not
necessarily rooted in aberrant or dysfunctional biological systems. Quite the contrary, sexual dysfunction caused by any number of different somatic, psychological, or interpersonal factors may respond positively to pharmacotherapeutic intervention. That is, any intervention targeted at the mechanics of ejaculation is likely to be effective in rectifying the genital component of the problem, independent of its cause [155].

8. EVALUATING TREATMENT

Because different types of treatment intervene at different stages in the dysfunctional response sequence in PE men, the choice of outcome measures depends partly on the specific treatment that is implemented. A treatment plan for PE, for example, may primarily address the endpoint of sexual satisfaction (e.g., with a somatically based problem in which pharmacological treatment is not an option). Alternatively, it could address ejaculatory latency (e.g., pharmacological treatment) which in turn affects sexual satisfaction, or it might address ejaculatory control (e.g., behavioral-cognitive techniques), which subsequently affects both ejaculatory latency and sexual satisfaction. For example, psychological-behavioral strategies instruct patients in the use of mental imagery, behavioral techniques (e.g., adjusting intercourse position, using pauses, etc.), and relationship interactions to develop greater control over the timing of ejaculation. In achieving such control, IELT would be lengthened and greater satisfaction attained. In this treatment, all three measures—ejaculatory control, IELT, and satisfaction—are relevant endpoints, as the focus of the intervention is on developing better ejaculatory control, which, in turn, affects both IELT and satisfaction. Indeed, in using all three measures, the researcher or clinician is better able to verify the specific processes through which sexual satisfaction, the ultimate endpoint, is affected.

In contrast, pharmacotherapeutic treatment is aimed at inhibiting the ejaculatory reflex and may not necessarily enable greater control over the timing of ejaculation other than by delaying it. But, as with any medical treatment in which the patient is a «passive» recipient of a treatment procedure, pharmacotherapy—in delaying the ejaculatory reflex—may give the man with PE a greater sense of control over his sexual problem. As a result, assessment of self-efficacy by using a measure such as «ejaculatory control» is perhaps less germane to pharmacotherapy studies than assessment of the other two characteristics of PE—ejaculation latency and general sexual satisfaction. Indeed, research indicates that while men who respond positively to the ejaculatory-inhibiting effects of clomipramine show substantial increases in both IELT and satisfaction, the effect on self-reported «ejaculatory control» tends to be modest.[76,156]. Nevertheless, assessment of self-efficacy in pharmacotherapy studies may be warranted, as increased self-efficacy is undoubtedly related to overall satisfaction with the treatment procedure. However, self-efficacy in such studies might be better assessed with items asking about «the ability to delay ejaculation» or «the ability to control/avoid early ejaculation» than with one that specifically assesses «ability to control ejaculation (or its timing).»

IV. PHARMACOLOGICAL TREATMENT OF PREMATURE EJACULATION

1. SELECTIVE SEROTONINE REUPTAKE INHIBITORS (SSRIs) (TABLE 5)

In 1943 Bernard Schapiro [103] described the use of topical anaesthetic ointment to delay ejaculation. The use of anaesthetics to diminish the sensitivity of the glans penis is probably the oldest form to treat early ejaculation. In 1973 the first report of successful ejaculation delay by clomipramine was published [157]. However, in the seventies and eighties of last century, drug treatment of early ejaculation was not very popular. The introduction of the selective serotonine reuptake inhibitors (SSRIs) meant a revolutionary change in the approach to and treatment of early ejaculation. Selective serotonine reuptake inhibitors encompass 5 compounds (citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) with a similar pharmacological mechanism of action. In 1994 the first double-blind study was reported on the ejaculation delaying effect of paroxetine [158]. In the last decade all other SSRIs and clomipramine have repeatedly been investigated in their propensity to delay ejaculation [159-179]. There is some evidence that fluvoxamine and citalopram have less effect in delaying ejaculation than paroxetine, sertraline and fluoxetine [166,169,177].

Although the methodology of the initial drug treatment studies was rather poor, later double-blind and placebo-controlled studies replicated the genuine effect of clomipramine and SSRIs to delay ejaculation. In spite of a development towards more eviden-
Based on evidence based drug treatment research the majority of studies still lack adequate design and methodology [72,180]. For the interpretation of drug treatment studies it is important to bear in mind that the outcome values of the ejaculation time are dependent on both gender (e.g. assessment by the male or his female partner) and method (e.g. assessment by subjective reporting, questionnaire, or stopwatch) [72]. A recent systematic review and meta-analysis of all drug treatment studies [180], clearly demonstrated that single-blind and open design studies and studies using subjective reporting or questionnaires showed a higher variability in ejaculation delay than double-blind studies in which the ejaculation delay was prospectively assessed with a stopwatch. Of all 76 studies only 11 studies (14.4%) [94,164,169,177-179],[181-185] have been performed according to the established criteria of evidence based medicine [180].

Nevertheless, in spite of the inaccuracy of most drug treatment studies to assess the delay accurately, there are 3 drug treatment strategies to treat early ejaculation: 1) daily treatment with serotonergic antidepressants 2) as-needed treatment with antidepressants and 3) anaesthetic topical ointments.
a) Daily treatment with serotonergic antidepressants

Daily treatment can be performed with paroxetine (20-40 mg), clomipramine (10-50 mg), sertraline (50-100 mg) and fluoxetine (20-40 mg). Meta-analysis of all drug treatment studies has demonstrated that paroxetine exerts the strongest ejaculation delay. Paroxetine, sertraline and fluoxetine may give rise to side effects like fatigue, yawning, mild nausea, loose stools or perspiration. These side effects often start in the first week after intake and gradually disappear within 2-3 weeks. Ejaculation delay with daily treatment usually manifests itself at the end of the first or second week and sometimes even earlier. With the exception of fluoxetine, it is advised not to stop the SSRIs acutely but gradually within 3-4 weeks, in order to avoid withdrawal symptoms. Side effects of clomipramine may consist of nausea, dry mouth and fatigue. Sometimes clomipramine and the SSRIs may give rise to reversible feelings of diminished libido or moderate decreased rigidity of the penis. It is advised to inform patients about all aforementionned side effects when starting treatment.

b) On-demand treatment with antidepressants

Since 1993 only 8 studies [76,99,156,186-190] on as-needed (on-demand) treatment have been published. Due to this limited number of studies and to inadequate designs, a meta-analysis is insufficiently powered to provide final conclusions with regard to difference in efficacy and dose-relationships. In spite of these scientific limitations it has been found that clomipramine (10-50 mg) taken minimally 4-6 hours prior to intercourse may be efficacious lasting for at least 15 hours. Another strategy is the daily use of paroxetine, sertraline and fluoxetine in a low dose combined with as-needed higher doses shortly before intercourse.

Based on the rating of the Level of Evidence of the studies reviewed, treatment of early ejaculation with the SSRI class drugs, paroxetine, sertraline, fluoxetine and citalopram, and the serotonergic tricyclic antidepressant, clomipramine, has a Grade A recommendation.

2. TOPICAL LOCAL ANAESTHETICS (TABLE 6)

Application of the topical anaesthetics to the penis virtually abolishes the display of penile reflexes in rats [191]. Sachs and Liu demonstrated that division of the sensory branches of the pudendal nerves severely impaired the ability of male rats to achieve intromission, and hence ejaculation [192]. Weidner reported that ejaculatory response to penile vibrotactile stimulation in spinal cord injured men requires the presence of intact dorsal penile nerves [193].

The use of topical local anaesthetics such as lignocaine and/or prilocaine as a cream, gel or spray is well established and they appear moderately effective in retarding ejaculation, but do so at the price of possibly causing significant penile hypo-anaesthesia, and possible transvaginal absorption, resulting in vaginal numbness and resultant female anorgasmia unless a condom is use [194-198]. Atan et al. reported the combined use of fluoxetine and topical lidocaine in 43 men with PE. Seventy two percent of the fluoxetine treated improved as opposed to 83.3 % of the fluoxetine/lidocaine group [199].

Xin et al. reported significantly improved ejaculatory control in 89.2% of patients treated with SS-cream [200,201]. SS-cream is made with extracts from nine natural herbs - Ginseng radix alba, Angelicae giganticae radix, Cistanchis herba, Zanthoxylli fructus, Torridis semen, Asiasari radix, Caryophylli flos, Cinnamoni cortex and Bufonis veneum. Some of these herbs have local anaesthetic properties. It is applied

<table>
<thead>
<tr>
<th>Reference No.</th>
<th>Author/s</th>
<th>Drug</th>
<th>Level of Evidence</th>
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<tbody>
<tr>
<td>184</td>
<td>Choi HK, Jung GW, Moon KH. et al</td>
<td>SS-Cream</td>
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<tr>
<td>195</td>
<td>Atikeler, M. K., Gecit, I., Senol, F. A</td>
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<td>196</td>
<td>Damru, F</td>
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<td>197</td>
<td>Berkovich, M., Keresteci, A. G., Koren, G</td>
<td>Prilocaine-lidocaine</td>
<td>1B</td>
</tr>
<tr>
<td>208</td>
<td>Sahin et al</td>
<td>Prilocaine-lidocaine</td>
<td>3B</td>
</tr>
<tr>
<td>209</td>
<td>Atan, A., Basar, M. M., Aydoganli, L</td>
<td>Fluoxetine, lidocaine</td>
<td>3B</td>
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<td>200</td>
<td>Xin, Z. C., Choi, Y. D., Choi, H. K</td>
<td>SS Cream</td>
<td>3B</td>
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<td>Xin, Z. C., Choi, Y. D., Lee, S. H. et al</td>
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<td>202</td>
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<td>SS Cream</td>
<td>1B</td>
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to glans penis 1 hour before and washed off immediately prior to coitus. Adverse effects were noted in 5.9% of patients which included mild local irritation and delayed ejaculation. Both the latency and amplitude of somatosensory evoked potentials measured at the glans penis were increased over baseline after the application of SS-cream [202].

Based on the rating of the Level of Evidence of the studies reviewed, treatment of early ejaculation with topical anaesthetics has a Grade A recommendation.

3. PHOSPHODIESTERASE INHIBITORS (TABLE 7)

Several authors have reported their experience with sildenafil citrate as a treatment for PE [188,190,203]. Abdel-Hamid et al. compared the efficacy and safety of the “on demand” clomipramine, sertraline, paroxetine, sildenafil and the pause/squeeze technique in the treatment of lifelong early ejaculation in a prospective randomised double blind crossover study of 31 potent men [188]. Treatment with sildenafil was associated with a significantly higher IVELT (15 minutes) and sexual satisfaction score than all other treatments and sexual satisfaction scores positively correlated with the IVELT for each treatment. The lack of a placebo group, the estimation of baseline IVELT by patient recall only and the use of the EDITS treatment response inventory which is validated for ED and not PE are major limitations of this study. Many men with entirely normal ejaculatory control will, as a result of inadequate sexual education and/or unrealistic patient/partner expectations incorrectly perceive themselves as “early ejaculators”.

In an open label study of 80 potent men, Salonia et al. compared treatment with paroxetine alone using initial chronic and then “on demand” dosing, with a combination paroxetine and sildenafil, using the same dosing regime for paroxetine and sildenafil administered one hour prior to intercourse [190]. Both treatments significantly improved the ejaculatory latency time and intercourse satisfaction domain of the IIEF. The combination of paroxetine and sildenafil produced superior results in both end points at 6 months treatment and the authors suggested a possible role of sildenafil in the treatment of early ejaculation.

Using a validated scoring inventory for the severity of PE, Chen et al. studied 58 men with PE who were previously refractory to psychosexual counselling and pharmacological treatment [203]. Treatment with sildenafil administered one hour prior to sexual intercourse significantly improved the baseline inventory score for the severity of PE. The authors suggest improved erectile function as the possible mechanism and a potential role of sildenafil in the treatment of early ejaculation. The proposed mechanisms for the effect of sildenafil of ejaculatory latencies include a central effect involving increased NO and reduced sympathetic tone, smooth muscle dilatation of the vas deferens and seminal vesicles which may oppose sympathetic vasoconstriction and delay ejaculation, reduced performance anxiety due to better erections and down regulation of the erectile threshold to a lower level of arousal allowing so that increased levels of arousal are required to achieve the ejaculation threshold. None of these studies are placebo controlled and the results are confusing and difficult to interpret. It is unlikely that phosphodiesterase inhibitors have a significant role in the treatment of PE with the exception of men with acquired PE secondary to co-morbid ED.

The results of a manufacturer sponsored double blind placebo controlled multicentre study have yet to be fully reported. Preliminary results show no significant difference in the IVELT of sildenafil compared to placebo but do demonstrate significant improvements in the ejaculatory control domain and the ejaculatory function global efficacy question. The latter is possibly consistent with the erectile response of sildenafil.

Based on the rating of the Level of Evidence of the studies reviewed, treatment of early ejaculation with Phosphodiesterase inhibitors has a Grade C recommendation.

<table>
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<th>Reference No.</th>
<th>Author/s</th>
<th>Drug</th>
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<tr>
<td>189</td>
<td>Chia SJ</td>
<td>Sildenafil</td>
<td>2B</td>
</tr>
<tr>
<td>190</td>
<td>Salonia, A., Maga, T., Colombo, R. et al.</td>
<td>Sildenafil</td>
<td>1B</td>
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</table>
Men with early ejaculation should be evaluated with a detailed medical and sexual history, a physical examination and appropriate investigations to establish the true presenting complaint, identify obvious biological causes such as medication or recent pelvic surgery, and uncover sufficient detail to establish the optimal treatment plan. (Figure 7)

Relevant information to obtain from the patient includes:

1. A basic medical history, including use of prescribed and recreational medications
2. The cultural context and developmental history of the disorder, including whether the rapid ejaculation is global or situational, lifelong or recent in its development,
3. Measures of the quality of each of the three phases of the sexual response cycle: desire, arousal, and ejaculation, since the desire and arousal phases may impact the ejaculatory response,
4. Details about the ejaculatory response, including the patient’s subjective assessment of his intravaginal ejaculatory latency time (IELT) and sense of ejaculatory control, the level of sexual dissatisfaction and distress, the frequency of sexual activity, and so on,
5. The partner’s assessment of the situation, including whether the partner suffers from female sexual dysfunction (FSD), and
6. Assessment of the sexual and overall relationship

Men with rapid ejaculation secondary to erectile dysfunction, other sexual dysfunction or genitourinary infection should receive appropriate etiology specific treatment. Men with lifelong rapid ejaculation should be managed with pharmacotherapy. Men with significant contributing psychogenic or relationship factors may benefit from concomitant behavioural therapy. Recurrence of rapid ejaculation is highly likely to occur following withdrawal of treatment. Men with acquired rapid ejaculation can be treated with pharmacotherapy and/or behavioural therapy according to patient/partner preference. Restoration of ejaculatory control in men with acquired rapid ejaculation is likely to occur following completion of treatment but is the exception in men with lifelong rapid ejaculation. Behavioural therapy may augment pharmacotherapy to enhance relapse prevention.

D. DELAYED EJACULATION, ANEJACULATION AND ANORGASMIA

Any psychological or medical disease or surgical procedure which interferes with either central control of ejaculation or the peripheral sympathetic nerve supply to the vas and bladder neck, the somatic efferent nerve supply to the pelvic floor or the somatic afferent nerve supply to the penis can result in delayed ejaculation, anejaculation and anorgasmia. As such, the causes of delayed ejaculation, anejaculation and anorgasmia are manifold (Table 8). The progressive loss of the fast conducting peripheral sensory axons which begins to be apparent in the third decade of life, and the dermal atrophy, myelin collagen infiltration and pacinian corpuscle degeneration observed in older men, may result in a degree of age related degenerative penile hypo anaesthesia.
PATIENT COMPLAINING OF PREMATURE EJACULATION (PE)

PATIENT/PARTNER HISTORY
- Establish presenting complaint
- Intravaginal Ejaculatory Latency Time
- Perceived degree of ejaculatory control
- Degree of patient/partner distress
- Onset and duration of PE
- Psychosocial history
- Medical history
- Physical Examination

MANAGE PRIMARY CAUSE

PE SECONDARY TO ED OR OTHER SEXUAL DYSFUNCTION

YES

NO

TREATMENT

ACQUIRED PE

First Line
BEHAVIOURAL THERAPY
- Stop/Start
- Squeeze Technique
- Sensate Focus
RELATIONSHIP COUNSELLING

Second Line
PHARMACOTHERAPY
- SSRI agents
- Topical anaesthetics

PATIENT PREFERENCE

OR
Combination Treatment

ATTEMPT GRADUATED WITHDRAWAL OF PHARMACOTHERAPY AFTER 6 TO 8 WEEKS

LIFELONG PE

TREATMENT

First Line
PHARMACOTHERAPY
- SSRI agents
- Topical anaesthetics

Second Line
BEHAVIOURAL THERAPY
- Stop/Start
- Squeeze Technique
- Sensate Focus
RELATIONSHIP COUNSELLING

OR
Combination Treatment

Figure 7: Management algorithm for premature ejaculation
and difficulty in achieving the ejaculatory threshold [65]. This is anecdotally exaggerated in men with ED treated with intracavernous pharmacotherapy and is often compounded by the loss of pelvic floor muscle tone seen in the similar aged, post-menopausal and often multiparous sexual partners of these men.

<table>
<thead>
<tr>
<th>Table 8. Causes of Delayed Ejaculation, Anejaculation and Anorgasmia</th>
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<tr>
<td><strong>Psychogenic</strong></td>
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<td>Wolffian duct abnormality</td>
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<td>Prune belly syndrome</td>
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<td><strong>Anatomic Causes</strong></td>
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<td>Transurethral resection of prostate</td>
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<td>Bilateral sympathectomy</td>
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<tr>
<td>Abdominal aortic aneurysmectomy</td>
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<tr>
<td>Para-aortic lymphadenectomy</td>
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<td><strong>Medication</strong></td>
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<td>Alpha-methyl Dopa</td>
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<td>Thiazide diuretics</td>
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<tr>
<td>Tricyclic and SSRI antidepressants</td>
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<td>Phenothiazine</td>
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<td>Alcohol abuse</td>
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1. PATHOPHYSIOLOGY

1. CONGENITAL DISORDERS

a) Mullerian duct obstruction

As the male foetus develops, the Mullerian ducts normally disappear from above downwards under the influence of Mullerian inhibitory factor (MIF) which is produced by the Sertoli cells in the primitive testis. Failure of complete absorption may leave a small Mullerian duct remnant at the lower end that lies between the ejaculatory ducts. The Wolffian (mesonephric) ducts are composed of three distinct areas. The upper part forms the epididymis and distal vas deferens, while the proximal vas deferens, seminal vesicle and ejaculatory duct are derived from the middle area. The most caudal part is the common mesonephric duct, from which the ureteric bud springs at approximately 4 weeks of development: this becomes the ureter, and will induce the metanephric blastema to form the kidney. The urogenital sinus reabsorbs the lower end of this structure, and the ureteric orifices are thus separated from the vasa deferentia, seminal vesicles and ejaculatory ducts. Several complex anomalies may occur in this area leading to ectopic opening of the vas deferens and sometimes associated with anorectal anomalies [204]. If too much of the proximal vas precursor is absorbed, a variable amount of the proximal vas, seminal vesicle and/or ejaculatory duct may be absent. There may also be coexisting abnormalities in the ipsilateral kidney or ureter.

Persistence of a small remnant of the Mullerian duct may lead to a cyst forming between the ejaculatory ducts which can become obstructed and cause diminution of the volume of the ejaculate and infertility. Haemospermia is not uncommon in these patients. Seminal analysis shows the changes characteristic of ejaculatory duct obstruction with a small volume (less than 1.5 ml), acid pH and little or no fructose. Both vasa are palpable and the epididymes usually feel distended. The diagnosis is established by transrectal ultrasound scan (TRUS), and the lesion can be delineated by percutaneous puncture of the cyst with instillation of radio-opaque medium (Figure 8). The cyst can be incised or deroofed endoscopically after delineating its extent by injection of blue dye (see below). Improvement in ejaculate volume and seminal quality follows in most cases [205].

b) Wolffian duct abnormalities

Congenital anomalies may be either sporadic, with a localized defect in the proximal part of the vas deferens or there may be a generalized maldevelopment due to a systemic genetic abnormality. Local Wolffian duct abnormality involves loss of a variable amount of the vas deferens, seminal vesicle and/or ejaculatory duct, and sometimes part of the ipsilateral urinary system as well. This may be associated with maldevelopment of the bladder neck and trigo-
ne, which fails to close effectively producing retrograde ejaculation.

Bilateral abnormalities are often associated with carriage of the cystic fibrosis gene [206]. Unilateral absence of the vas deferens was observed in 5%, and bilateral absence in 18% of 370 azoospermic males with normal serum FSH levels investigated by the author [207].

c) Prune Belly syndrome

Patients with prune belly syndrome have normal libido, erections, and orgasms. Most have abnormal ejaculation and probably emission. In a study involving nine patients, seven had retrograde ejaculation and two produced ejaculates [208]. Five patients provided semen or urine passed after masturbation. Two produced ejaculated semen. One of the ejaculated specimens consisted of 4.5 cc of fluid indistinguishable from urine and one was 2.5 cc of fluid with the appearance of watery semen. Post masturbation urine specimens were of normal urinary appearance. None of the specimens contained sperm: no mention was made of the fructose content. Abnormal ejaculation thus appears to be present in the vast majority of patients with prune belly syndrome. Whether the primary abnormality is retrograde ejaculation or lack of emission is not clear.

2. TRAUMATIC DAMAGE

a) Imperforate anus

Ejaculatory duct obstruction may follow correction of imperforate anus. The pull through procedure passes close to the posterior aspect of the prostate, and damage is most likely if there has been closure of a recto-urethral fistula. Analysis of 20 subfertile males who had repair of imperforate anus in infancy indicated that 7 had no ejaculate, 11 were azoospermic, 1 was severely oligozoospermic and only 1 had a normal sperm concentration in a very small volume ejaculate [209]. Investigation revealed that both vasa were blocked in 5 men and one vas in a further 8 patients, apparently as a result of the original operative procedure.

b) Operations on the prostate

Antegrade ejaculation requires a closed bladder neck (and proximal urethra). Surgical procedures that compromise the bladder neck closure mechanism may result in retrograde ejaculation. Transurethral incision of the prostate (TUIP) results in retrograde ejaculation in 5% [210] to 45% [211] of patients and is probably related to whether one or two incisions are made and whether or not the incision includes primarily the bladder neck or extends to the level of the verumontanum. The importance of contraction of the urethral smooth muscle at the level of the verumontanum has been hypothesized to be important in preventing retrograde ejaculation [212]. Transurethral resection of the prostate (TURP) carries a higher incidence of retrograde ejaculation than does TUIP. The reported incidence of retrograde ejaculation following TURP ranges from 42% [213] to 100% [214]. Although these men may have some antegrade ejaculation and usually experience orgasmic sensation, both may be reduced as part of the changes that occur in the male sexual response as a man ages. Retrograde ejaculation and failure of emission can be distinguished by examination of a post masturbatory specimen of urine for the presence of spermatozoa and fructose.

After radical prostatectomy, ejaculation is bound to be lost since the seminal vesicles are removed with the prostate gland. Erectile impotence was the rule until detailed anatomical studies showed where the parasympathetic nerves ran on the surface of the prostate gland, and a nerve sparing operative technique was developed [215]. A sensation of orgasm is often preserved despite loss of ejaculation.

Retrograde ejaculation can be surgically treated with bladder neck reconstruction but results remain consistently poor [215]. Drug treatment is the most promising approach. As mentioned earlier, alpha-adrenergic sympathetic nerves mediate both bladder neck closure and emission. Several sympathomimetic agents have been described as useful with mixed results [216]. These drugs include pseudoephedrine and ephedrine, and phenylpropanolamine. These agents work by stimulating the release of noradrenaline from the nerve axon terminals but may also directly stimulate both alpha- and beta-adrenergic receptors. The most useful is pseudoephedrine which is administered at a dose of 120 mg 2-2.5 hours pre-coital. The tricyclic antidepressant, Imipramine which blocks the reuptake of noradrenaline by the axon from the synaptic cleft is also occasionally useful [217]. The usual dose is 25mg twice daily. Current feeling is that long-term treatment with imipramine is likely to be more effective. Whilst medical treatment may not always produce normal ejaculation it may result in some prograde ejaculation. In patients who do not achieve antegrade ejaculation with either surgery or medication, sperm retrieval and artificial insemination is an alternative approach. The basic method of sperm retrieval involves reco-
very of urine by either catheter or voiding after masturba-
tion, and then centrifugation and isolation of the sperm.

3. INFECTIVE DISORDERS

Genital infection such as gonorrhoea or non-specific urethritis can produce cicatrization and obstruction anywhere in the male reproductive tract, especially if treatment is delayed. Urinary infection, especially if complicated by epididymitis, can also produce obstruction that may be situated at ejaculatory duct level. Routine vasography in subfertile men with azoospermia and normal serum FSH levels revealed post-infective vasal blocks in 8% and acquired ejaculatory duct obstruction in 4% [207]. Schistosomiasis is endemic in large parts of Africa, and is seen with increasing frequency in tourists returning from Africa who have contracted the disease whilst enjoying water sports. The disease may present with haematospermia [218] and fibrosis and calcification may lead to genital obstruction. Genito-urinary tuberculosis can cause great damage to the male reproductive tracts, and since healing occurs with calcification, the lesions may be irreparable. Plain X-ray will often show the extent of the disease.

Haematospermia is seldom as ominous a symptom as haematuria, but this complaint should not be ignored. Analysis of the findings in 81 patients revealed that an inflammatory cause could be defined in most men under 30 years of age; however, there were a few (8%) with more serious disease including carcinoma of prostate and bladder [219].

It should be remembered, also, that schistosomiasis and tuberculosis could present in this way. Routine investigation of haematospermia by TRUS not uncommonly reveals the presence of small stones in the ejaculatory ducts, which may be associated with obstruction and dilatation of the seminal vesicles. Such stones usually pass spontaneously.

4. NEUROLOGICAL DISORDERS

a) Spinal cord Injury

The ability to ejaculate is severely impaired by spinal cord injury (SCI). Bors and Comarr highlighted the impact of the level and completeness of SCI on the post injury erectile and ejaculatory capacity (Table 9) [220,221]. Unlike erectile capacity, the ability to ejaculate increases with descending levels of spinal injury. Less than 5% of patients with complete upper motor neuron lesions retain the ability to ejaculate. Ejaculation rates are higher (15%) in patients with both a lower motor neuron lesions and an intact thoracolumbar sympathetic outflow. Approximately 22% of patients with an incomplete upper motor neuron lesion and almost all men with incomplete lower motor neuron lesions will retain the ability to ejaculate. In those patients who are capable of successful ejaculation, the sensation of orgasm may be absent and retrograde ejaculation often occurs.

Several techniques for obtaining semen from spinal cord injured men with ejaculatory dysfunction have been reported. The intrathecal administration of anticholinesterase inhibitors neostigmine and subcutaneous physostigmine to induce ejaculation is more of historical interest and is no longer used due to a 60% risk of autonomic dysreflexia, especially in men with injuries above the T5 level [222,223]. Vibratory stimulation is successful in obtaining semen in up to 70% of men with spinal cord injury [224]. This technique induces a reflexogenic ejaculation via the sacral roots and the ejaculatory coordination centre in the upper thoracolumbar spinal cord. The use of electro-ejaculation to obtain semen by electrical stimulation of efferent sympathetic fibres of the hypogastric plexus is an effective and safe method of obtaining semen. Brindley have reported that 71% of men with spinal cord injury who underwent electro-ejaculation achieved ejaculation [225]. However,

<table>
<thead>
<tr>
<th>Cord Lesion</th>
<th>Reflexogenic Erections (%)</th>
<th>Psychogenic Erections (%)</th>
<th>Successful Coitus (%)</th>
<th>Ejaculation (%)</th>
</tr>
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<td>Incomplete</td>
<td>0</td>
<td>1</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 9. Correlation of erection, ejaculation and intercourse with level and severity of spinal cord injury [87]
both are associated with a significantly higher risk of autonomic dysreflexia than electro-ejaculation. Pre-treatment with a fast acting vasodilator such as nifedipine will minimise the risk of severe hypertension should autonomic dysreflexia occur with either form of treatment [226]. If the spinal reflex arc is intact, a hypogastric plexus stimulator can provide ejaculation in the comfort and security of the patients’ home [227]. Percutaneous aspiration of semen from the vas deferens has also been reported as a means of harvesting semen for use with artificial reproductive techniques [228].

Semen collected from men with spinal cord injury is often initially senescent and of poor quality with a low sperm count and reduced sperm motility but may improve with subsequent ejaculations. This poor semen quality may be due to chronic urinary tract infection, sperm content with urine, chronic use of various medications, elevated scrotal temperature due to prolonged sitting and stasis of prostatic fluid. Testicular biopsies in spinal cord injured men demonstrate a wide range of testicular dysfunction including hypospermatogenesis, maturation arrest, atrophy of seminiferous tubules, germinal cell hypoplasia, interstitial fibrosis and Leydig cell hyperplasia. In addition prostatitis secondary to prolonged catheterisation, epididymitis and epididymo-orchitis can precipitate obstructive ductal lesions and testicular damage. Ohl et al reported that sperm density and motility were higher in those with incomplete lesions [229]. In a recent collective analysis of 40 paraplegic patients, 22 successfully produced pregnancies by natural insemination or assisted reproductive techniques [230].

5. FUNCTIONAL DISORDERS

a) Seminal megavesicles

Adult polycystic kidney disease has been found in association with pathological dilatation of the seminal vesicles in 6 patients [235]. TRUS and percutaneous puncture of the seminal vesicles before and after resection of the ejaculatory ducts revealed that the gross dilatation of the seminal vesicles was not caused by obstruction, but appeared to be due to atonicity (megavesicles). These ultrasonic appearances, when described previously, were incorrectly thought to be due to seminal vesicle cysts. Pathological dilatation of the seminal vesicles in the absence of obstruction has been described previously, although the aetiology remains obscure [236].

b) Para-aortic lymphadenectomy

This operation is usually done to clear lymph node metastases from testicular tumours, when the sympathetic nerves and ganglia may also be removed leading to loss of ejaculation. Early studies showed that up to three-quarters of patients lost antegrade ejaculation after full bilateral retroperitoneal lymph node dissection. As a result of careful anatomical studies, the technique of retroperitoneal lymph node dissection has been modified with nerve sparing so that antegrade ejaculation is now maintained in 70-90% of patients.

One quarter of the patients who complete chemotherapy for advanced testicular tumour have residual masses in the para-aortic region [231]. Amongst 231 consecutive patients undergoing para-aortic lymphadenectomy after chemotherapy at the Royal Marsden Hospital, there was persistent undifferentiated tumour in 21% [232]. In our experience of 186 patients, a nerve sparing operative technique introduced in 1984 lead to a significant reduction in ejaculatory dysfunction from 37% to 19% [233]. Loss of ejaculation occurred significantly more often after bilateral (46%) compared to unilateral (14%) dissection, and was related to the size of the excised mass (<4 cm 4%; 4-8 cm 19%; >8 cm 60%).

It is important to anticipate this complication in young men with testicular tumours who may need chemotherapy or node dissection, and arrangements should be made for sperm storage before treatment commences. Excellent results can be obtained with artificial insemination using cryopreserved spermatozoa [234].

5. FUNCTIONAL DISORDERS

a) Seminal megavesicles

Adult polycystic kidney disease has been found in association with pathological dilatation of the seminal vesicles in 6 patients [235]. TRUS and percutaneous puncture of the seminal vesicles before and after resection of the ejaculatory ducts revealed that the gross dilatation of the seminal vesicles was not caused by obstruction, but appeared to be due to atonicity (megavesicles). These ultrasonic appearances, when described previously, were incorrectly thought to be due to seminal vesicle cysts. Pathological dilatation of the seminal vesicles in the absence of obstruction has been described previously, although the aetiology remains obscure [236].

b) Radiotherapy for male pelvic cancer

Quality of Life (QoL) in general and sexual functioning in particular have become very important in cancer patients. Due to modern surgical techniques, improved quality of drugs for chemotherapy and very modern radiation techniques, more patients can be successfully treated without largely compromising sexual functioning (Table 10).

• Prostate cancer

Prostate cancer (PC) has become the most common non-skin malignancy in men in Western countries. External-beam radiotherapy (EBRT) and brachytherapy (BT) are together with the radical prostatectomy (RP) the most common and effective treatments for localized PC. Regardless of the introduction of very modern radiotherapy (RT) techniques, sexual functioning after PC treatment remains problematic for many patients. Self-administered questionnaires
have widely been used to evaluate sexual functioning in patients after RT of PC. Nevertheless, such instruments are highly variable and largely unvalidated. These questionnaires elicited limited information about aspects of sexuality other than erectile function. Although a deterioration of sexual activity has been associated with the severity of ejaculatory dysfunction, particularly a decrease in volume or absence of semen [237], only a few questionnaires included items related to ejaculation and orgasm.

Already in the 1980s ejaculatory disturbances following RT of PC were reported [238]. In the 1990s more studies included items related to desire, ejaculation and orgasm. After EBRT, a decline in sexual desire was reported by 43% of 64 patients, a decreased frequency of orgasm by 57%; all men reported a decrease in ejaculate volume [239]. By using a validated questionnaire, Borghede and Sullivan [240] reported a decrease in the ability to ejaculate in 56% of the patients. Good prognostic factors for sexual functioning preservation following RT were low age and higher frequency of intercourse.

Also in early BT studies sexual functioning was assessed. Herr [241] reported already in 1979 on 51 patients treated with retropubic Iodium-125 seeds. Loss of ejaculate was experienced by 6% of the patients. In a later study dry ejaculation was reported by 16% of the patients after BT [242]. In both studies, all patients had previously undergone a transurethral resection of the prostate (TURP). For the first time a discomfort with ejaculation was mentioned in two studies (up to 25% of the patients) [243, 244]. This is quite common in clinical practice after BT; it is due to edema of the prostate possibly reducing the elasticity of the urethra and inducing discomfort with ejaculation. In some patients discomfort with ejaculation did not disappear even 18-24 months after BT [245]. Also decreased interest in sex and sexual desire, and libido was mentioned in up to 50% of the patients evaluated [240, 244-246].

There are a few data on the etiology of post-RT decreased libido and ejaculatory disorders. Daniell et al. [247] studied retrospectively levels of testosterone (TST) and other hormone after RT of PC. TST was found to be low 3 to 8 years after EBRT. Lower levels were found in older patients. Although testes are very sensitive to radiation, spermatogenesis is more easily affected than androgen productions. The radiation dose calculated in the testes of men irradiated for PC is only 3-8% of the dose that could possibly affect androgen production and explain a decrease in TST. A TURP carries a high incidence of retro-

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Table 10. Level of Evidence - Radiotherapy for male pelvic cancer

<table>
<thead>
<tr>
<th>Reference No.</th>
<th>Author/s</th>
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<th>Level of Evidence</th>
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<tr>
<td>239</td>
<td>Helgason AR, Fredrikson M, Adolfsson J, et al.</td>
<td>Prostate</td>
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<td>240</td>
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<td>241</td>
<td>Herr HW</td>
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<td>241</td>
<td>Kwong EWH, Huh SH, Nobler MP, et al.</td>
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<td>Kleinberg L, Wallner K, Roy J, et al.</td>
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<td>1</td>
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<td>Daniell HW, Clark JC, Pereira SE, et al.</td>
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<td>248</td>
<td>Bonnel C, Parc YR, Pocard M, et al.</td>
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<td>Schover LR, Gonzales M, von Eschenbach AC.</td>
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<td>251</td>
<td>Jonker-Pool G, van Basten JP, Hoekstra HJ, et al.</td>
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<td>252</td>
<td>Tinkler SD, Howard GCW, Kerr GR</td>
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<td>253</td>
<td>Caffo O, Amichetti M</td>
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<tr>
<td>234</td>
<td>Scammell GE, White N, Stedronska J et al.</td>
<td>Testicular</td>
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</tr>
</tbody>
</table>
grade ejaculation because it is thought to disrupt the closure mechanism of the vesical neck; this could explain ejaculatory disturbances in most patients following RT with previous TURP.

c) Rectal carcinoma

Not much is known about sexual functioning following RT of rectal carcinoma. Pre-operative RT for rectal cancer has been associated with a reduction in the rate of local relapse, and possibly an advantage in survival. Pre-operative RT with the total mesorectal excision (TME) in low stage rectal cancer has become a common procedure in Europe. A sharp dissection of the mesorectum associated with visualization and preservation of the pelvic autonomic nerve leads to excellent results regarding erectile and ejaculatory functioning. Only one study has specifically studied the effects of pre-operative RT for rectal carcinoma on male sexual functioning and concluded that it may impair male sexual functioning [248]. Numbers were too small to draw final conclusion.

d) Testicular cancer

Germ cell tumors of the testis are relatively rare accounting for about 1% of all male cancers. The long-term survival for early disease approaches 100%. Because testicular cancer affects mainly young men in their sexual and fertile life, sexual functioning and ejaculatory disorders are particularly important. The side effects of retroperitoneal lymph node dissection (RPLND) for residual mass after chemotherapy for non-seminomatous cancer are better documented than sexual sequelae of elective abdominal RT for seminoma.

Dry ejaculation occurs in the majority of the patients in non-nerve sparing techniques. As a result of careful anatomical studies, the technique of RPLND has been modified with nerve sparing so that antegrade ejaculation is now maintained in 80-100% of patients [249]. Libido and orgasm seem to be normal in these patients.

Following RT a deterioration in sexual functioning has been reported between 1% and 25% of the patients [250-254]. Tinkler et al. reported on 237 patients after orchectomy and abdominal RT and compared these data to 402 age-matched controls [252]. In almost all parameters studied including erection, ejaculation and libido, patients scored less than controls (reduction in orgasm, in libido, and interest in sex). Specifically, there was no difference in the ability to ejaculate during sexual activity but the RT patients reported a noticeable reduction in the amount of semen compared to before treatment [252]. Caffo et al. evaluated toxicity and QoL of 143 patients treated for early-stage testicular cancer [253]. Twenty-three per cent reported a decreased libido, 27% problems with getting an orgasm and 38% ejaculation disturbances, including early ejaculation (PE).

A decrease in sexual desire, in orgasm and volume or semen was negatively correlated with age [250]. Jonker-Pool et al [251] reported on three groups of patients, after RT, wait and see, and chemotherapy. RT patients reported decreased libido in 22% compared to 12% in the wait and see group and 30% in the chemotherapy group. Decrease of absence of ejaculation was reported in 15%, 7% and 21% in the three groups, respectively; decreased orgasm in 15%, 12% and 30%, respectively. Although the differences are not statistically significant, in the RT group ejaculation and orgasm disturbances are higher than in the wait and see group. Similar results were reported by Arai et al.[237].

PE was reported in up to half of the patients [237,254], but it was the same as recalled before treatment [254]. The superior hypogastric plexus is responsible for ejaculation and it is mediated by the sympathetic system; it is a fenestrated network of fibres anterior of the lower abdominal aorta.

The hypogastric nerves exit bilaterally at the inferior pole of the superior hypogastric plexus, and have connections with the S1-S2 roots. Normal emission requires integrity of this system. During RPLND these nerves are difficult to recognize and might be damaged, resulting in decreased semen volume or dry ejaculation. Pathways for ejaculation are included in the RT fields for rectal and prostate carcinomas.

A damage of the sympathetic nerves could be caused by radiation, but the dose does not seem enough to completely explain the dysfunction. Orgasm is even more complex than ejaculation since it is also affected by cortical input. Drug treatment for loss of ejaculation is not very successful but electroejaculation can produce spermatozoa for insemination.

It is important to anticipate this complication in young men with testicular tumors who may need chemotherapy or node dissection. Arrangements should be made for sperm collection and storage at the earliest opportunity before treatment commences. Excellent results can be obtained with artificial insemination using cryopreserved spermatozoa [234].
E. INHIBITED EJACULATION (IE)

This section describes the definition, incidence, etiology, and treatments for inhibited ejaculation (IE), commonly known as delayed or retarded ejaculation. The literature contained few randomized clinical trials and despite the consensus conference’s strong preference for evidence based medicine, adequate summarizing of the etiological and treatment literature currently requires inclusion of expert opinion, anecdotal and case study information, at this time. Generally speaking, the information presented and the interventions described may produce beneficial results, but further evidence and evaluation is required. The specifics are delineated below and point the way toward the necessary future research, which is summarized at the conclusion of this sub-chapter.

I. NOSOLOGY, DEFINITION AND DESCRIPTION OF INHIBITED EJACULATION (IE)

There are multiple terms used to describe a delay or absence of male orgasmic response. Retarded ejaculation, delayed ejaculation and inhibited ejaculation as well as idiopathic anejaculation, primary impotence ejaculationis, and psychogenic anejaculation have all been used essentially synonymously to describe this problem in men. Like the term “early ejaculation,” the most commonly used term “retarded ejaculation” is often avoided because of its pejorative associations. This sub-chapter will use the initials IE, but the reader should understand that as of this moment all investigators agree on what is being named, but not the name itself.

The Diagnostic and Statistical Manual of Mental Disorders, 4th edition [69] defines inhibited ejaculation (IE) as the persistent or recurrent difficulty, delay in, or absence of attaining orgasm following sufficient sexual stimulation, which causes personal distress. Parenthetically, partially retarded ejaculation is sometimes observed in men who attempt to control a early ejaculation by suppressing the muscular contractions associated with ejaculation. They experience diminished pleasure and sensation as semen is released during emission, but the ejaculatory sensations are dulled through over control of striated muscle. Failure of ejaculation can be a lifelong primary event (e.g., congenital anorgasmia) or an acquired or secondary problem. It can happen in every sexual encounter or it may be intermittent. Some men with secondary IE can masturbate to orgasm; others, for a multiplicity of reasons, would or could not masturbate. Some men lose masturbatory capacity secondary to emotional or physical trauma. Some men have reported intermittent nocturnal emissions, and others were either unaware of or did not have - an orgasm nocturnally. Coital anorgasmia was usually an issue for the extremely religious (e.g., Ultra-Orthodox Jews) referred for fertility problems, although this was not the case for other men who were distressed by their inability to orgasm in response to manual or oral stimulation by their partner.

- Incidence

Since the beginning of sex therapy, IE was seen as a clinical rarity and difficult symptom to treat.[277] Masters and Johnson [86] reported only 17 cases, while Apfelbaum [277] reported 34 cases, and Kaplan [278] fewer than 50 cases, in the history of their practices. Perelman [279] reported over 100 cases, including both primary and secondary RE. Simons & Carey [280] reviewed 52 studies showing “community samples indicate a current prevalence of “0-3% for male orgasmic disorder” versus 4%-5% for early ejaculation.” They indicate that clinic populations may be characteristically higher. The popularity of urologic-based treatments for erectile dysfunction has resulted in an anecdotally reported, clinically observed, unexpected increase in men suffering from IE [279]. IE, like other sexual dysfunctions, is also likely to become more prevalent with the aging of the world population [281].

II. ETIOLOGY

IE is not yet well understood and there are a number of etiological explanations, offering both psychological and somatic explanations.

1. Drug induced

It has been well known for years that adverse sexual side effects of many drugs and alcohol cause delayed or fully impaired orgasm in men and women (Table 5) [282-284]. This was especially true of psychotrophic medications [283,285-289].

2. Biological variability

In addition to psychodynamic and interpersonal
causes for IE, a biological etiology should also be considered. There is strong likelihood of biological variability in the threshold of arousal necessary before experiencing orgasm. Furthermore, it seems likely that the dispersal pattern of ejaculatory latency should resemble the same bell shaped distribution as do so many other human characteristics. Extrapolating from Waldinger’s laboratory rat research, individuals experiencing either early ejaculation (PE) or IE are likely to be biologically predisposed to their symptom. The dysfunction becomes manifest given certain external factors: medications, sexual circumstances, and intra- and interpersonal dynamics, etc [279,290]. One could speculate that normal variation in the function of the nervous systems responsible for ejaculation could result in a somatically determined variation between men’s ejaculatory latency and capacity. Explanation of biologic predisposition is often helpful by itself in reducing patient and partner anxiety and mutual recriminations, while simultaneously assisting the formation of a therapeutic alliance with the health care professional [279].

3. CULTURAL AND PSYCHOLOGICAL ETIOLOGIES

a) Religious/culture.

Masters & Johnson [86] first indicated that IE was associated with orthodoxy of religious belief. Beliefs may limit sexual experience necessary for developing the knowledge necessary to learn to ejaculate or may result in an inhibition of normal function. Regardless of specific religion involved (Muslim, Hindu, Jewish, etc.), many devout religious men have masturbated only minimally or not at all. Some of these men masturbated for a period of years like their secular counterparts, but guilt and anxiety about “spilling seed” often resulted in idiosyncratic masturbatory patterns, which in turn resulted in IE. These men often had little contact with women prior to marriage (which may have been arranged after a few chaperoned dates). These very religious men may date, but were less likely than their secular counterparts to experience orgasm with a partner, especially through intercourse. Some of these men did sexually experiment with women who they did not marry; however, their cognitions about these women often reflected a «Madonna-whore» split.

b) Concurrent psychopathology

Multiple explanations for IE have been offered, with unconscious aggression and unexpressed anger recurring as themes in the IE literature [291-294]. Additionally, pregnancy fears received emphasis, since the reason for professional referral is often the female partner’s wish to conceive. Finally, Bancroft’s [295] model of psychogenic factors in erectile dysfunction depending on a delicate balance between central excitatory and inhibiting mechanisms would seem to have potential applicability to the understanding of IE as well.

c) Insufficient sexual arousal

An excellent critical review of the psychological etiology of IE was provided by Apfelbaum [277], who provocatively first noted the sexual politic surrounding IE and female anorgasmia: “Like the women who has inappropriately been castigated for willfully depriving her husband of the pleasure of bringing her to orgasm. The retarded ejaculator’s own belief that he is withholding is widely endorsed, understandably by his partners and less justifiably by most therapists”. Not only psychoanalysts, but sex therapists and behavior therapists as well, seemed to assume the IE patient’s orgasm is blocked, rather than the patient’s level of arousal being insufficient.

Apfelbaum [277] observed that some males appeared able to achieve erections sufficient for intercourse despite a relative absence of subjective arousal. He felt these “automatic erections” were taken as erroneous evidence by both the male and his partner that the man was ready for sex and capable of achieving orgasm. This same process is the likely cause of increased anecdotal clinical reports of IE for patients using popular urologic-based treatments for ED [2, 296]. Urologists received a few early complaints of IE, secondary to successful penile prosthesis surgery and ICI. However, Sildenafil brought huge numbers of patients to physician’s offices. Many of these patients experienced restored erections and coitus with ejaculation. While Sildenafil has been used with some success to facilitate reversal of the antidepressant sexual adverse effects [297], the effect of PDE 5 inhibitors may be bimodal [2,296]. The phenomena of erection without adequate psychoemotional arousal occurred in some men using sildenafil when they did not experience sufficient erotic stimulation before and during coitus. These men confused their erect state as an indication of sexual arousal when, it merely indicated vasocongestive success [2, 296].

d) Masturbation

Apfelbaum [277] coined autosexual orientation to describe men with IE who prefer masturbation to partnered sex. Perelman [296] discussed the role of
fantasy, as well as masturbation frequency, motivation, and idiosyncratic technique in the etiology and maintenance of IE. Many men with IE engage in stimulation that was striking in the speed, pressure, duration, and intensity necessary to produce an orgasm, and dissimilar to what they experienced with a partner. In this manner, they have preconditioned themselves to likely difficulty with a partner and experience secondary IE. Disparity between the reality of sex with the partner and the sexual fantasy (whether unconventional or not) used during masturbation is another cause of IE. This disparity takes many forms: body type, orientation, sex activity performed, etc. Many men and women remain inhibited about using their masturbatory fantasies when with their partner. Yet like their female counterparts, when anorgasmic men integrate their masturbatory fantasies into sex with their partner, orgasm is more likely [296].

e) Mixed etiology

It would seem that IE, like other sexual dysfunctions, is best understood as being caused by an interaction of both organic and psychogenic factors. A biological set point for ejaculatory latency is impacted upon by multiple organic and psychogenic factors in varying combinations over the course of a man’s life cycle. Appropriate assessment requires an appreciation of how each of these factors determines the endpoint dysfunction for a particular individual, at a particular moment in time.

III. EVALUATION

Assessment begins by reviewing the conditions under which the man is able to ejaculate, e.g., during sleep, with masturbation, with partner’s hand or mouth stimulation or infrequently with varying coital positions. The course of the problem is documented, and variables that improve or worsen performance are noted. Questions concerning the man’s ability to relax, sustain, and heighten arousal and the degree to which he can concentrate on sensations are posed [298]. If orgasmic attainment had been possible previously, the life events/circumstances temporarily related to orgasmic cessation are reviewed. The events in question maybe pharmaceutical, illness, or a variety of life stressors and other psychological factors e.g. following his wife’s mastectomy: the man is afraid of hurting her and therefore only partially aroused. Societal/religious attitudes that may interfere with excitement are noted, such as the spilling of seed as a sin. Finally, questions concerning the quality of the nonsexual relationship are posed and problems explored. This assessment in conjunction with appropriate physical examination and laboratory results will provide understanding and determine an appropriate treatment path.

Haematospermia requires full investigation. Culture of expressed prostatic secretion and urine will define the nature of an infective process such as prostatitis [299] and urine cytology and serum prostate specific antigen should be assayed to exclude bladder or prostatic cancer. Ultrasound scan of the testicles and epididymes should define any local disease. TRUS will demonstrate structural abnormality in the prostate or seminal vesicles, or may show up a stone in the ejaculatory duct or even a Mullerian duct cyst. Cystoscopy is seldom helpful.

If a man has difficulty with ejaculation, or has a small volume or absent ejaculate, it must first be established whether the problem is congenital or acquired. A careful clinical history should be taken, and physical examination will establish whether the testicles and epididymes are normal, and whether the vasa are present or absent, on each side. Next, it is essential to establish whether there is retrograde or completely absent ejaculation, by examination of a deposit of urine after centrifugation. The presence of spermatozoa indicates retrograde ejaculation. These facts will allow the patient to be placed into one of several broad categories, after which more detailed evaluation can take place.

Patients with ejaculatory duct obstruction usually present with infertility. Seminal analysis may simply be reported a showing azoospermia or oligozoospermia, but the characteristic biochemical changes should be sought. There should be absence of part or the entire component of the ejaculate that comes from the vasa and seminal vesicles via the ejaculatory ducts. The volume is low (usually less than 1.5 ml), the pH is low (less than 7) and the fructose content is either low (less than 120 mg/100ml) or absent. If both vasa are palpable, a diagnosis of ejaculatory duct obstruction is very likely.

When there is absence of the vasa, it is important to establish whether the condition is unilateral or bilateral. With unilateral absence of the vas deferens, the urinary system must also be checked by ultrasound scanning, as coexisting renal anomalies may be present [300]. With bilateral absence or malformation of the vasa, it is essential to consider whether the anomaly may be part of a genetic defect associated with carriage of the potentially harmful cystic fibrosis chromosome anomaly [206].
1. Imaging in Ejaculatory Duct Obstruction

The lesion may be suspected by finding distended seminal vesicles on transrectal ultrasound scanning. However, the exact site of obstruction should be defined radiologically by vasography or percutaneous puncture of the seminal vesicles (Figures 8, 9). Subsequently, methylene blue dye may be instilled to outline the ejaculatory system so that it can be recognized after it has been entered at transurethral resection [301].

2. Electrophysiological Evaluation of the Nervous Pathways Controlling Ejaculation

Neurophysiological tests allow objective evaluation of the nervous pathways controlling ejaculation and are occasionally of use in the evaluation of delayed ejaculation or anejaculation. Four tests are routinely used.

a) Pudendal Somatosensory Evoked Potentials (Pudendal SEPs)

Somatosensory evoked potentials (SEPs) are defined as a transient alteration of the EEG following peripheral nerve stimulation. They provide objective information concerning the afferent volley from the dorsal nerve of penis to the cortex. The technique consists of electrical stimulation of the dorsal nerve of penis with recording of the evoked responses over the spine and the scalp (2 cm behind the central vertex). First the sensibility threshold is measured. By definition, the sensibility threshold is the lowest perceivable sensation of the electrical current at the point of stimulation. The latency of the response is measured both at the onset of the response and the peak of the first reproducible deflection. By recording the response at 2 different levels, 3 different transit times are obtained: a total transit time (from penis to brain), a peripheral transit time (from penis to spine), and a central transit time (which is obtai-
ned by subtracting the peripheral from the total transit time). The peripheral transit time is approximately 13.5 ms. The total transit time is approximately 34 msec (onset) and 43 msec (top of P1 deflection) [302, 303].

b) Pudendal motor evoked potentials (Pudendal MEPs)

Motor Evoked Potentials (MEPs) explore the efferent pathways (pyramidal tracts) from brain to target muscle (bulbocavernous muscles). The technique consists of stimulating the motor cortex and sacral roots by means of a magneto-electric stimulator. For brain stimulation, the coil is applied 2 cm behind the vertex. For sacral root stimulation, the coil is applied laterally to the spine. The response is picked up from the bulbocavernous muscles with co-axial EMG needle electrodes. Brain stimulation is performed, first at rest, and then during a voluntary contraction of the pelvic floor (facilitation procedure). Sacral root stimulation is performed only at rest. The response is measured at the onset of the first reliable deflection. By stimulating the central nervous system at 2 levels, 3 different transit times will be obtained: a total transit time (from brain to target muscle), a peripheral transit time (from sacral roots to target muscle) and a central transit time (obtained by subtracting the peripheral from the total transit time). The total transit time measured in the bulbocavernous muscles is respectively 28 msec (brain stimulation patient at rest) and 23 msec (brain stimulation patient contracting the pelvic floor). The peripheral transit time is 7 msec (sacral root stimulation).[304]

c) Sacral reflex arc testing: the somatic-somatic reflex arc

The test allows the investigation of the sensory and motor branch of the pudendal nerve and of the sacral segments S2, S3, S4. The technique consists in stimulating the dorsal nerve of the penis and recording the response from the bulbocavernous muscles. The response consists usually of 2 deflections. The mean latency of the first deflection is 35 msec, although a late deflection is often observed at 80 msec [303, 305].

d) Sympathetic Skin Responses (SSRs)

Electrical activity from the sympathetic nerve terminals controlling the sweat glands of the skin can be recorded following electrical stimulation of any peripheral nerve trunk. The test allows evaluation of the sympathetic efferent outflow to the skin of the genital organs. The dorsal nerve of the penis is stimulated using 2 ring electrodes wrapped around the penile shaft, the cathode being proximal.

The stimulation consists of single electrical pulses applied at a rate of 0.05 Hz. Sympathetic skin responses are recorded from hand, foot, and perineum using disc electrodes affixed to the skin. Two tracings are superimposed to check the reproducibility of the response. The right median nerve is then stimulated, and SSRs are recorded from the hand, foot, perineum, and penis. The mean latency of hand, foot, and perineum SSRs following dorsal nerve of the penis stimulation are, respectively, 1.40 sec, 2 sec, and 1.4 sec. Following median nerve stimulation, the latency of penile SSRs is 1.50 sec [306, 307].

IV. TREATMENT

Treatment should be etiology specific and address the issue of infertility in men of a reproductive age.

1. Psychological treatment for inhibited ejaculation

Heiman and Meston’s [138] summary of sex therapy treatments concluded that “inadequate data” on the topic of delayed orgasm in men prevented any conclusion regarding efficacy of treatment. However, many treatments for IE have been suggested in the psychotherapy literature, including early psychodynamic and sex therapy approaches [86,301,308-312]. Masters and Johnson [86] reported a low failure rate of 17.6% using a treatment combination of sensate focus, vigorous non-coital penile stimulation and modifications of intercourse technique. In the Ohl, et al. study, 81% of men who were anorgasmic prior to fertility treatment were successful in reaching orgasm through vibrator stimulation.[313] Apfelbaum [277] treated almost all of his RE cases with «body work» using sexual surrogates. Perelman [296] reported retrospective chart review success rates of over 80% in treating IE using a cognitive-behavioral sex therapy. However, these were uncontrolled case reports with treatment ranging from a few brief sessions of sex education to the nearly two years of multiple-modality treatment in more complex multiple etiologic cases.

Numerous drugs, herbs and medication dosing strategies have been reported to offset an iatrogenic induced, antidepressant-related IE. Widespread use of selective serotonin reuptake inhibitors (SSRIs) in the last decade has triggered tremendous interest in
the effect of these antidepressants on sexual function [288,314]. Additionally, case reports indicated successful use of sildenafil to treat SSRI-induced orgasmic latency problems in men and women, with clinical trials currently investigating this phenomenon.[283,315,316] Recently, Nurnberg et al. [297] published a prospective, parallel-group, randomized, double-blind, placebo-controlled multi-center in order to assess the efficacy of sildenafil citrate in men with sexual dysfunction associated with the use of selective and nonselective serotonin reuptake inhibitor antidepressants. In this study, sildenafil effectively improved erectile function and other aspects of sexual function in men with sexual dysfunction associated with the use of SSRI antidepressants. While the endpoints used were very limited, regarding the question of ejaculatory latency, this is one of the few RCT studies to address this question and accordingly becomes important. It remains to be seen whether sildenafil will be shown to be an orgasmogenic agent, however, it is probable that multiple compounds will be developed to reduce orgasmic threshold and assist us in treating people who have difficulty reaching orgasm. Indeed, some speculate that a dopaminergic pathway might facilitate orgasm.

2. DRUG TREATMENT

Whilst retrograde ejaculation can be surgically treated with bladder neck reconstruction, no surgical procedure exists for the treatment of failed emission. As is the case with retrograde ejaculation, drug treatment is the most promising approach. Whilst medical treatment may not always produce normal ejaculation it may convert a patient with lack of emission into one with retrograde ejaculation and may result in small amounts of viable sperm both of which can be combined with standard artificial insemination techniques to produce a pregnancy.

There are multiple reports in the literature of the use of a variety of drugs in the treatment of delayed ejaculation or anejaculation (Table 11). The drugs facilitate ejaculation by either a central dopaminergic or anti-serotonergic mechanism of action. There are not published placebo controlled studies and most are anecdotal case reports/series that dealing with the treatment of SSRI induced ejaculatory dysfunction.

Several authors have reported that the cerebral serotonergic system exerts an inhibitory role on ejaculation and male sexual activity in the rat model and that the dopaminergic system, particularly that in the anterior hypothalamus, has a facilitatory role [317, 318]. The ejaculatory dysfunction commonly associated with the anti-hypertensive alpha-methyldopa which reduces cerebral monoamine levels by suppressing the cerebral dopaminergic system is consistent with these reports [176]. The occurrence of paradoxical hyper sexuality, e.g. spontaneous orgasm, with clomipramine and fluoxetine, however, suggest

<table>
<thead>
<tr>
<th>Reference No.</th>
<th>Author/s</th>
<th>Drug</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>321</td>
<td>McCormick, S., Olin, J., Brotman, A. W</td>
<td>Cyproheptadine</td>
<td>4</td>
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<tr>
<td>322</td>
<td>Ashton, K., Hamer, R., Rosen, R</td>
<td>Cyproheptadine</td>
<td>2B</td>
</tr>
<tr>
<td>323</td>
<td>Feder, R</td>
<td>Cyproheptadine</td>
<td>4</td>
</tr>
<tr>
<td>324</td>
<td>Lauerma, H</td>
<td>Cyproheptadine</td>
<td>4</td>
</tr>
<tr>
<td>325</td>
<td>Lauerma, H</td>
<td>Cyproheptadine</td>
<td>4</td>
</tr>
<tr>
<td>326</td>
<td>Aizenberg, D., Zemishlany, Z., Weizman, A</td>
<td>Cyproheptadine</td>
<td>4</td>
</tr>
<tr>
<td>329</td>
<td>Balon, R</td>
<td>Amantadine</td>
<td>4</td>
</tr>
<tr>
<td>330</td>
<td>Shrivastava, R., Shrivastava, S., Overweg, N. et al.</td>
<td>Amantadine</td>
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<tr>
<td>331</td>
<td>Valevski, A., Modai, I., Zbarski, E. et al.</td>
<td>Amantadine</td>
<td>4</td>
</tr>
<tr>
<td>332</td>
<td>Gitlin, M. J</td>
<td>Amantadine</td>
<td>4</td>
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<tr>
<td>333</td>
<td>Balogh, S., Hendricks, S., Kang, J</td>
<td>Amantadine</td>
<td>4</td>
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<tr>
<td>334</td>
<td>Price, J., Grunhaus, L. J</td>
<td>Yohimbine</td>
<td>4</td>
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<tr>
<td>335</td>
<td>Jacobsen, F. M.</td>
<td>Yohimbine</td>
<td>4</td>
</tr>
<tr>
<td>336</td>
<td>Hollander, E., McCarley, A.</td>
<td>Yohimbine</td>
<td>4</td>
</tr>
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<td>337</td>
<td>Witkin, J. M., Perez, L. A.</td>
<td>Buspirone</td>
<td>4</td>
</tr>
<tr>
<td>338</td>
<td>Othmer, E., Othmer, S. C</td>
<td>Buspirone</td>
<td>4</td>
</tr>
<tr>
<td>339</td>
<td>Cooper, B. R., Hester, T. J., Maxwell, R. A</td>
<td>Bupropion</td>
<td>4</td>
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<tr>
<td>340</td>
<td>Ashton, A., Rosen, R.:</td>
<td>Bupropion</td>
<td>4</td>
</tr>
<tr>
<td>342</td>
<td>Aizenberg, D., Gur, S., Zemishlany, Z. et al.:</td>
<td>Mianserin</td>
<td>4</td>
</tr>
</tbody>
</table>
that this balance is more complex and that different 5-HT receptor subtypes may have opposing effects on sexual function [297,319,320].

The antihistamine, cyproheptadine which increases cerebral serotonin levels, has been shown to increase male sexual activity in the rat [317]. The literature contains several anecdotal case reports and other small case series of the use of cyproheptadine to reverse the anorgasmia induced by the SSRI antidepressants but contains no controlled studies [321-326]. These studies suggest an effective dose range of 2-16mg., administration on a chronic or "on demand" basis. McCormick (1995) reported the use of cyproheptadine to reverse the anorgasmia induced by the SSRI fluoxetine has been reported in 2 patients [321]. Ashton et al. also reported improvement in 12 of 25 men with SSRI induced sexual dysfunction with a mean dose of 8.6mg with efficacy limited by sedation and potential reversal of antidepressant effect [322]. The author’s experience suggests a role for cyproheptadine in the treatment of both retarded ejaculation and anejaculation which is limited to a degree by its sedative effect.

Central dopamine activity can be increased by a variety of mechanisms ranging from the provision of dopamine synthesis precursors e.g. L-dopa, to use of substitute neurotransmitters to directly stimulate central dopamine receptors (Tables 12, 13). Amantadine, an indirect stimulant of dopaminergic nerves both centrally and peripherally, which is used in the treatment of Parkinson’s disease and has a limited role as an anti-viral agent, has been reported to stimulate sexual behaviour, ejaculation and other sexual reflexes in rats [327,328]. Several authors have reported a place for amantadine in the reversal of SSRI antidepressant induced anorgasmia [322,329-333]. Ashton et al. reported improvement in SSRI induced sexual dysfunction in 8 of 19 men with mean dose of 200mg.[322] Balon reported some efficacy with "on demand" amantadine (100mg) administered 5-6hrs before coitus in a similar group of patients [329]. Several authors have reported their experience with Yohimbine, a derivative of the bark of the Yocon tree, in the management of SSRI induced sexual dysfunction [334-336]. Yohimbine is an alpha-2 antagonist, an alpha-1 agonist, a calcium channel blocker and inhibits platelet aggregation. Price and Grunhaus reported reversal of clomipramine-induced anorgasmia with a dose of 10mg administered 90 minutes

Table 12 Adjunctive Drug Therapy for SSRI-Induced Sexual Dysfunction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Symptom</th>
<th>Dosage</th>
</tr>
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<tbody>
<tr>
<td>Amantadine</td>
<td>Anorgasmia, Decreased libido, Erectile dysfunction</td>
<td>100-400 mg (for two days prior to coitus) 75-100 mg bid or tid</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Anorgasmia</td>
<td>75-150 mg 75 mg bid or tid</td>
</tr>
<tr>
<td>Buspirone</td>
<td>Anorgasmia, Decreased libido, Erectile dysfunction</td>
<td>15-60 mg 5-15 mg bid</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>Anorgasmia, Decreased libido, Erectile dysfunction</td>
<td>4-12 mg On Demand</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>Anorgasmia, Decreased libido, Erectile dysfunction</td>
<td>5.4-10.8 mg 5.4 mg tid</td>
</tr>
</tbody>
</table>

Table 13. Mechanism of Action of Drugs which increase Dopamine Neurotransmission

<table>
<thead>
<tr>
<th>Mechanism of Increasing Dopamine Neurotransmission</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolong action by decreasing uptake</td>
<td>bupropion, cocaine</td>
</tr>
<tr>
<td>Prolong action by decreasing metabolism</td>
<td>l-deprenyl</td>
</tr>
<tr>
<td>Increased release of dopamine</td>
<td>amphetamine</td>
</tr>
<tr>
<td>Direct stimulation of DA receptors with substitute neurotransmitters</td>
<td>bromocriptine, quinelorane, apomorphine</td>
</tr>
<tr>
<td>Increase Dopamine synthesis by providing precursors</td>
<td>L-dopa</td>
</tr>
</tbody>
</table>
prior to coitus [334]. In a placebo-controlled study of 15 patients with fluoxetine-induced anorgasmia, Jacobsen reported a 73% response rate to yohimbine [335]. Hollander reported that yohimbine reversal of anejaculation in 5 of 6 men with intercourse and/or masturbation [336]. The response to yohimbine is typically delayed taking up to 8 weeks and is often associated with adverse effects including nausea, headache, dizziness and anxiety. Careful dose titration is important as the extremes of dose have less pro-sexual effect.

Buspirone is a benzodiazepine class anxiolytic which possesses 5HT-1A receptor agonist activity [337]. Othmer et al. reported normalization of sexual function in 8 of 10 men with a generalized anxiety disorder and associated sexual dysfunction using a dose range of 15-60mg daily [338]. Bupropion is a novel antidepressant which prolongs the action of dopamine by reducing its uptake from the synaptic cleft [339]. Ashton and Rosen described reversal of SSRI induced anorgasmia in 66% of patients studied. An improvement in sexual function was noted by Rowland in 14 non-depressed diabetic men with ED with «on demand» doses of 75-150 mg [340].

Several authors have reported induction of «early ejaculation» in rats following administration of apomorphine, a central and peripheral DA-2 receptor agonist, at a dose of 50mcg/kg. DA receptor antagonists block this effect [262,341]. Aizenberg et al. examined the effect of the 5-HT2a/2c and alpha 2 antagonist mianserin in the treatment of patients with sexual dysfunction induced by serotonin reuptake inhibitors (SSRIs) [342]. Nine of the 15 subjects reported a marked improvement in their sexual functioning in the areas of orgasm and satisfaction usually within the first and second week of mianserin treatment. The authors suggested that co administration of low-dose mianserin might be an additional option in the treatment of sexual dysfunction induced by SSRIs.

Quinelorane is a highly selective, potent DA-2 agonist, which was extensively studied in animals in the early part of this decade. Foreman and Hall observed increased mounting, intromission and ejaculation in both sexually inactive and sluggish rats following administration of quinelorane [343]. Prior administration of a dopamine antagonist eliminated these stimulatory effects confirming that these sexual effects were due to stimulation of DA receptors. They reported that many rats failed to ejaculate at the extremes of doses with low doses causing sedation and high doses causing hyperactive behaviour such as chewing or sniffing. Animals appears to become more sensitive to dopamine agonists with increased use, suggesting that abuse may eliminate any sexual benefits. Eaton et al. injected quinelorane directly into the rat paraventricular nucleus and medial preoptic area and reported different response with different doses [344]. At extremes, quinelorane could cause paradoxical PE, reduced sexual desire and ED. The reduced sexual response observed at low doses is due to stimulation of dopamine «auto- receptors» which decrease dopamine activity and respond to lower doses than do the stimulatory DA-2 receptors. In theoretical clinical use, lowering the dose to avoid excessive excitement may result in worse sexual dysfunction than prior to treatment. Human double blind placebo controlled clinical studies of quinelorane were commenced in late 1980s involving multiple sites and more than 500 men and women with ED, reduced sexual desire and reduced arousal. The United States Food and Drug Administration review of the trial data was inconclusive and concern was expressed over the more than 50% incidence of nausea and hypotension and the indirect negative sexual adverse effects. Clinical studies were terminated and the results remain confidential and unpublished.

Based on the rating of the Level of Evidence of the studies reviewed, pharmacological treatment of delayed ejaculation or anejaculation has a Grade C recommendation (Table 11).

V. OFFICE MANAGEMENT OF DELAYED EJACULATION, ANEJACULATION AND ANORGASMIA

Men with delayed ejaculation, anejaculation and/or anorgasmia should be evaluated with a detailed medical and sexual history, a physical examination and appropriate investigations to establish the true presenting complaint, identify obvious biological causes such as medication or recent pelvic surgery, and uncover sufficient detail to establish the optimal treatment plan. (Figure 10)

Relevant information to obtain from the patient includes:

1. A basic medical history, including use of prescribed and recreational medications

2. The cultural context and developmental history of the disorder, including whether the ejaculatory
dysfunction is global or situational, lifelong or recent in its development,

3. Measures of the quality of each of the three phases of the sexual response cycle: desire, arousal, and ejaculation, since the desire and arousal phases may impact the ejaculatory response,

4. Details about the ejaculatory response, including the presence or absence of orgasm, the prodromal sensation of ejaculatory inevitability and prograde ejaculation, the level of sexual dissatisfaction and distress, the frequency of sexual activity, and so on,

5. A careful physical examination to establish whether the testicles and epididymes are normal, and whether the vasa are present or absent, on each side

6. The partner’s assessment of the situation, including whether the partner is suffering from female sexual dysfunction (FSD), and

7. Assessment of the sexual and overall relationship

Treatment should be etiology specific and address the issue of infertility in men of a reproductive age. Men who never achieve orgasm and ejaculation, are suffering from either a biogenic failure of emission and/or psychogenic inhibited ejaculation. Management involves identification of the etiology and disease specific treatment. Men who occasionally achieve orgasm and ejaculation are usually suffering from psychogenic inhibited ejaculation or penile hypoanaesthesia secondary to age related degeneration of the afferent penile nerves. The former is managed with behavioural therapy and/or psychotherapy. Men with age related penile hypoanaesthesia should be educated, reassured and be instructed in revised sexual techniques which maximise arousal.

The majority of men who always achieve orgasm but never experience prograde ejaculation or have a greatly reduced prograde ejaculatory volume, have retrograde ejaculation. The presence of spermatozoa and fructose in centrifuged post-ejaculatory voided urine confirms the diagnosis. Management involves education and reassurance of the patient, pharmacotherapy or, in rare cases, bladder neck reconstruction. The absence of spermatozoa suggests congenital absence or agenesis of the testis or vas/vasa or acquired ejaculatory duct obstruction. Management involves investigation by ultrasonic or radiological imaging to identify the site of obstruction and disease specific treatment.

VI. THE FUTURE

The management of inhibited ejaculation is likely to evolve towards combination treatment using integrated pharmacotherapy and sex therapy approaches. It seems likely that the most effective treatments for IE will follow the pattern seen in the treatment of ED, where an integration of pharmacotherapy and sex therapy is becoming the treatment of choice [297,345-355]. These recent articles by urologists and sex therapists have advocated a multidisciplinary approach for the treatment of ED; emphasizing the importance of follow-up in providing opportunity for necessary patient education and counseling. Additionally, the integration of sexual counseling and pharmacotherapy is likely to be of assistance to patients seeking adjustment and rehabilitation from multiple medical conditions (e.g., retrograde ejaculation secondary to prostatic surgery). Furthermore, couples presenting multiple sexual dysfunctions are likely to benefit from a model incorporating additional sex therapy with pharmacotherapy. An integrated model allows for resolving and balancing significant intra and interpersonal psychological issues which otherwise may destabilize treatment success. There are published case reports integrating sex therapy and pharmacotherapy when treating a couple’s multiple dysfunctions (including IE), but large controlled prospective studies are needed in order to define an appropriate treatment algorithm.[356] The development of new pharmaceuticals will only refine such an algorithm and improve our opportunity for enhancing orgasmic function.
Figure 10: Management algorithm for delayed ejaculation, anejaculation and anorgasmia

- **FAILURE OF EMISSION**
  - Neurogenic
  - Metabolic
  - Drug Adverse Effect
    → Disease Specific Management

- **DELAYED EJACULATION\  \ANEJACULATION\  \ANORGASMIA**
  → INHIBITED MALE ORGASM
    → Psychosexual therapy

- **INHIBITED MALE ORGASM**
  Nocturnal/Masturbation Emissions
  → Psychosexual Therapy

- **AGE RELATED DEGENERATION**
  → Reassure/alter sexual technique

- **NEVER**
  IS THERE ORGASM?
  → SOMETIMES
  → INHIBITED MALE ORGASM

- **IS THERE EJACULATION?**
  → ARE SPERM PRESENT IN URINE AFTER ORGASM?
    → YES
      → ASPERMIA
        → Ejac.Duct Obstruction
    → NO
      → RETROGRADE EJACULATION
        → Reassure/Educate
        → Pharmacotherapy
        → Surgery

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