Pharmacy Benefits
Management
Strategic Healthcare
Group and the Medical
Advisory Panel

The Primary Care Management of Erectile Dysfunction

Department of Veterans Affairs
Veterans Health Administration
Publication No. 99-0014
June 1999

Department of Veterans Affairs

Memorandum

Date:

From: Acting Under Secretary for Health (10)

Subj: Clinical Practice Guideline for Erectile Dysfunction

To: VISN Directors, VISN Clinical Managers, Medical Center Directors, Chiefs of Staff and Patient Care Staffs

1. To date, VHA has approved nine Pharmacologic Management Algorithms for the most common diseases associated with the veteran patient population (these documents may be referenced at *http://www.vapbm.org* or *http://vaww.pbm.med.va.gov*), while one additional Pharmacologic Management Algorithm and one Clinical Practice Guideline are being reviewed for approval.

2. Subsequent to the recent interest in the treatment of erectile dysfunction, the VA Pharmacy Benefits Management Strategic Healthcare Group (PBM) and the VA Medical Advisory Panel (MAP) were asked to coordinate a multidisciplinary effort to produce a document which would provide guidance to the Primary Care practitioner in the diagnosis and treatment of erectile dysfunction.

3. The attached document, *The Primary Care Management of Erectile Dysfunction*, is a departure from previous PBM / MAP efforts in that it incorporates more detailed information in the diagnosis portion of the document than would a PBM / MAP Pharmacologic Management Algorithm.

4. This guideline is based on nationally recognized treatment guidelines, current literature and expert opinion from clinicians across the VA system. These guidelines are dynamic and will be revised as new clinical data becomes available. Also, these guidelines are not intended to interfere with clinical judgement that might dictate deviation under special circumstances. Rather, they are intended to assist practitioners in providing consistent, high quality care.

5. I commend the efforts put forth in the development of these guidelines and know from the many comments received from throughout the VA that they are a welcome tool for both practitioners and managers. I strongly encourage their utilization and will closely follow their implementation, as well as the outcomes associated with their use. They constitute a significant advancement in VHA's evolution toward a truly integrated healthcare delivery system.

Thomas L. Garthwaite, MD

THE PRIMARY CARE MANAGEMENT OF ERECTILE DYSFUNCTION

Table of Contents **Page**

PBM Publication No. 99-0014 June 1999
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The Medical Advisory Panel for the Pharmacy Benefits Management Strategic Healthcare Group

Mission

The mission of the Medical Advisory Panel (MAP) for Pharmacy Benefits Management (PBM) includes the development of evidence-based pharmacologic management guidelines for improving quality and providing best-value patient care.

The MAP is comprised of practicing VA physicians from facilities across the nation:

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PBM Publication No. 99-0014 June 1999
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Pharmacy Benefits Management (PBM)
Strategic Healthcare Group (SHG)

VHA's PBM SHG has been directed by the Under Secretary for Health to coordinate the development of guidelines for the pharmacologic management of common diseases treated within the VA, establish a national level VA formulary, and to manage pharmaceutical costs, utilization, and measure outcomes as they apply to patient care. The MAP provides support and direction to the PBM staff, located in Hines, Illinois.

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PBM Publication No. 99-0014 June 1999
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Development of the Primary Care Management of Erectile Dysfunction

Whenever possible, the PBM and MAP relies upon evidence-based, multidisciplinary, nationally recognized consensus statements for the basis of VA Guidelines. Relevant literature is reviewed and assessed with consideration given to the VA population. Draft documents are sent to the field for comments prior to being finalized.

A group of clinical experts in the area of erectile dysfunction (ED) was convened to develop the ED guidelines. The Erectile Dysfunction Committee consisted of healthcare professionals from a variety of sub-specialties including: urology, endocrinology, ophthalmology, internal medicine, spinal cord injury, cardiology, psychology, medical/ethical specialist, nursing, physician assistance and pharmacy. The committee met with weekly teleconferences to discuss the literature and various issues.

Literature searches were conducted (e.g. Medline, NIH, etc.) with additional peer reviewed literature obtained by members according to their specialty. The general algorithm was developed first, followed with the specialty areas. Each specialist led his or her particular area of expertise. The committee worked in concert writing and reviewing the different annotations. If there were questions regarding any aspect of the guidelines, a literature search was re-run, information re-evaluated and this process repeated until consensus was obtained. The level of evidence and strength of recommendations were reviewed for each annotation, discussed and graded as a committee.

Development of the guidelines relied upon University Healthsystem Consortium Review, American Urologic Association Guidelines, The American College of Cardiology and the American Heart Association Guidelines, the National Institutes of Health, the American Academy of Ophthalmology, Human Sexuality
by Masters and Johnson (1995), the International Index of Erectile Function, the American Association of Clinical Endocrinologists and the Massachusetts Male Aging Study. The Agency for Health Care Policy and Research (publication No. 93-0550, March 1993) tool was used for grading Levels of Evidence and Strength of Recommendations.

Use of this document

The purpose of the guidelines is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. This guideline attempts to define principles of practice, which should produce high quality patient care. They are attuned to the needs of a primary care practice but are directed to providers at all levels. This document also serves as a basis for monitoring local, regional and national patterns of pharmacologic care.

Guidelines are not considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the same results. The ultimate judgment regarding the propriety of any course of conduct must be made by the clinician in light of individual patient situations.

Updating this document

PBM will review the guidelines routinely. Updating will occur as new information is made available from well-designed, scientifically valid studies and as outcome data may direct. Any member of the VA community is encouraged to recommend changes based on such evidence. A current copy of the guidelines can be obtained from the Pharmacy Benefits Management home page at *http://www.dppm.med.va.gov.*

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Referencing this document

This document should be referenced as:
Pharmacy Benefits Management-Medical Advisory Panel. The Primary Care Management of Erectile Dysfunction. VHA PBM-SHG Publication No. 99-0014. Hines, IL: Pharmacy Benefits Management Strategic Healthcare Group, Veterans Health Administration, Department of Veterans Affairs. June 1999.

Strength of Recommendations and Levels of Evidence Tables

The referenced articles have been assigned a grade of evidence and strength of recommendation rating, which is based on AHCPR guideline development (Agency for Health Care Policy and Research publication No. 93-0550, March 1993). For a description of each, refer to the following tables:

Level of Evidence Grading

Type of Evidence	**Level of Evidence Grading = A**	**Level of Evidence Grading = B**	**Level of Evidence Grading = C**
Primary evidence	Large, randomized controlled trials with clear-cut results (low risk of error) **Level 1**	Small, randomized trials with uncertain results (moderate to high risk of error) **Level 2**	Nonrandomized, contemporaneous controls; nonrandomized, historical and expert opinions; uncontrolled studies, case series, expert opinions and panel consensus **Levels 3, 4, 5**

Strength of Recommendation

Grade	**Strength of Recommendation**
I	Usually indicated, always acceptable, and considered useful and effective.
IIa	Acceptable, of uncertain efficacy, and may be controversial. Weight of evidence is in favor of usefulness/efficacy.
IIb	Acceptable, of uncertain efficacy and may be controversial. May be helpful, not likely to be harmful.
III	Not acceptable, of uncertain efficacy and may be harmful. Does not appear in the guidelines.

Algorithms

The symbols used in the algorithm are described below:
***Oval* –** Represents the start of the algorithm that defines the patient population.
***Rectangle* –** Represents a process, such as a diagnostic or therapeutic intervention.
Hexagon – Represents the point where a decision needs to be made.
Circle – Represents the point where the algorithm terminates or refers to another algorithm.

Acknowledgments

The PBM/MAP collaborated with VA technical advisory groups and other experts in developing this document. We gratefully acknowledge and thank those clinicians for sharing their expertise in this area.

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PBM Publication No. 99-0014 June 1999
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EXECUTIVE SUMMARY

1. The attached document discusses the evaluation and management of erectile dysfunction (ED) for primary care providers. It addresses the non-pharmacologic and pharmacologic management of ED, which includes the use of sildenafil (Viagra®). Please refer to VA policy regarding the use of sildenafil in the treatment of ED.

2. Erectile dysfunction is defined by the National Institutes of Health as being "the inability of the male to attain and maintain erection of the penis sufficient to permit satisfactory sexual intercourse". It is estimated that 50% of males over the age of 40 will have some degree of ED. The Department of Veteran Affairs cares for approximately 3.4 million veterans with an estimated average age of 58.4 years. It can therefore be concluded that approximately 1.7 million of these veterans may have some form of ED. The impact of this medical condition is significant to the VA from a patient and treatment perspective.

3. Erectile dysfunction may be the result of one or more of the following conditions: medication side effects, endocrine disorders, peripheral vascular disease, neurologic dysfunction, penile diseases, psychological disorders, and lifestyle factors. Once ED is diagnosed, each of these potential causes must be carefully addressed prior to initiating treatment.

4. Patients with ED should have a thorough medical history and physical examination to identify etiologies and co-morbidities. Cardiovascular and ophthalmologic evaluations require particular attention in considering patients for sildenafil therapy. Along with these exams, the International Index of Erectile Function (IIEF) or a similarly validated sexual function questionnaire may be used to document severity of ED. Limited laboratory testing may be indicated.

5. Patient health education (PHE) is a necessary component for the successful treatment of ED. Education of the patient and partner should include information on the causes, the risk factors, the misconceptions about ED, the treatments available for ED and their associated benefits and risks.

6. A variety of treatment options, including counseling, mechanical devices, pharmacological treatment and surgical interventions, are available to VA patients. Not all therapies will be effective for every patient. It is the responsibility of the healthcare provider to discuss treatment options and assist the patient in choosing a satisfactory treatment plan.

7. The Erectile Dysfunction Guideline Committee has significant concerns about the safety of sildenafil in many VA patients. The University HealthSystem Consortium Review reached a similar conclusion, based on safety. Studies performed by the manufacturer do not reflect the demographics of the VA population.

8. A variety of new treatments for ED are currently under development. The Pharmacy Benefits Management Strategic Healthcare Group reviews new pharmacological treatments and makes recommendations for policy on a continual basis.

PBM Publication No. 99-0014 June 1999
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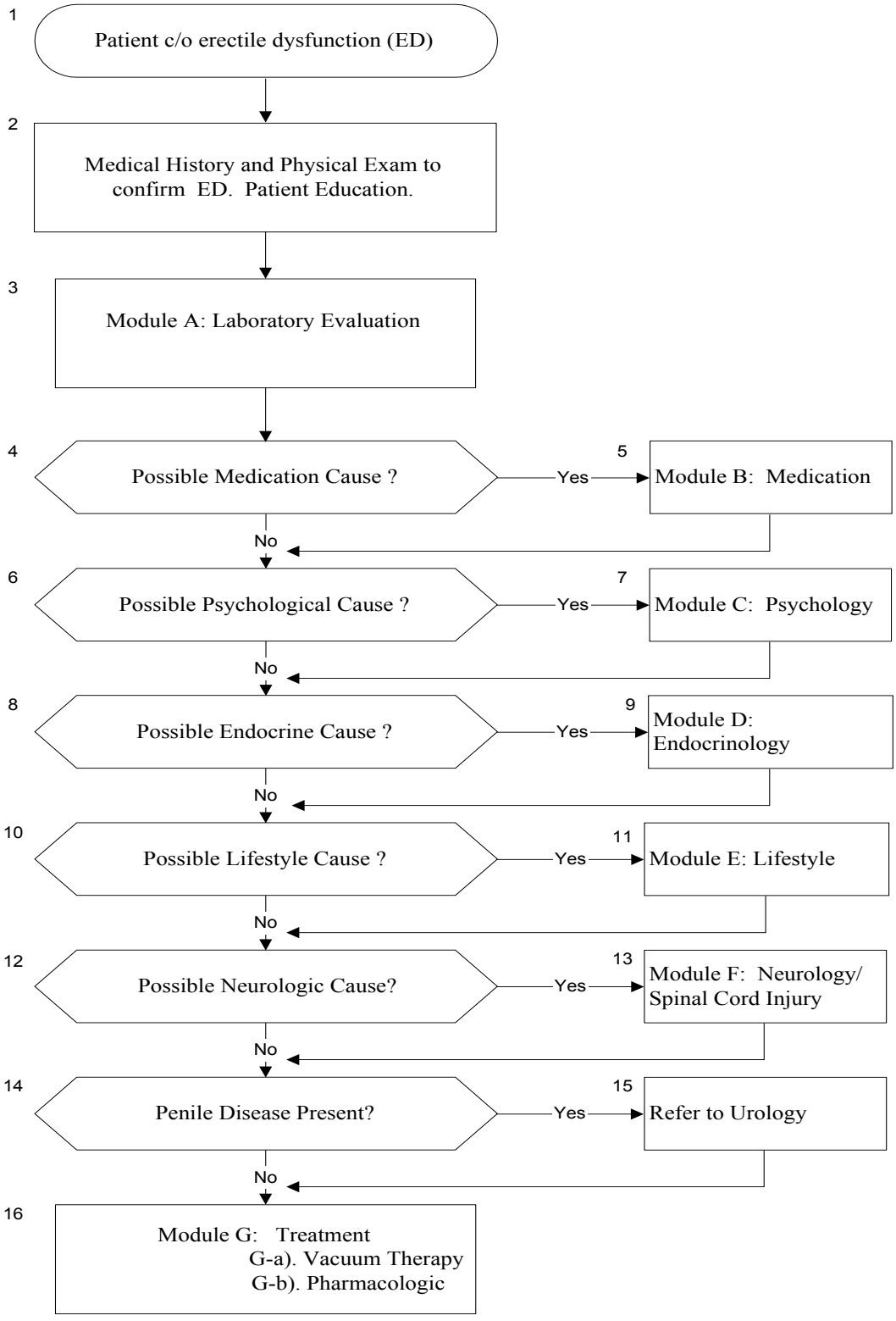
General Algorithm



PBM Publication No. 99-0014 June 1999
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Box 2. Medical History and Physical Exam to Confirm Erectile Dysfunction (ED). Patient Education.

Objective: Describe the critical elements of the history and physical exam which will assist a provider in evaluating a patient with erectile dysfunction (ED). Describe the importance of patient education.

Summary Annotation: Identification of the etiology of a patient's ED is critically dependent on the history and physical exam.(1-3) An essential first step is a thorough sexual, medical and psychosocial history. A focused physical exam emphasizing the genito-urinary, vascular and neurologic systems follows and complements the history. Greater emphasis should be placed on examining systems in which symptoms or complaints were elicited during the history. Findings from the history and physical examination may provide a diagnosis or aid in selecting further testing/evaluation.

Discussion: An essential first step in the evaluation of ED is a thorough sexual, medical and psychosocial history. A sexual history should include past and current aspects of a patient's erectile and sexual function. Quantifying the degree of erectile dysfunction as to severity, onset, duration and progression helps to suggest certain etiologies. A history of altered libido, ejaculation, orgasm, penile sensation or pain should be assessed. Equally important is an assessment of the partner's sexual function to include arousal, orgasm, libido and pain/vaginismus. A useful tool for the assessment of ED is the International Index of Erectile Function (IIEF). Appendix 1 describes the IIEF and its role in assessing ED.

The medical history should include questions searching for possible risk factors for ED and medical conditions associated with ED. An assessment of patient medications (e.g. antihypertensives, antidepressants) and recreational drug use (cocaine, alcohol) should be made. Is there a history of atherosclerotic peripheral or cardiovascular disease? Are risk factors for atherosclerosis present (diabetes, hypertension, hypercholesterolemia, family history of early atherosclerosis, or smoking)? Chronic medical conditions such as anemia, renal failure, and diabetic neuropathy should be noted. Prior surgeries (radical prostatectomy, laminectomy, vascular surgery) as well as any history of pelvic, perineal or penile trauma should be elicited. Younger patients with ED should be specifically questioned about bicycle riding, which may cause a reversible form of ED due to perineal trauma. Neurologic illness such as spinal cord injury or disease (multiple sclerosis), endocrinologic illness (hypogonadism, hyperprolactinemia, thyroid disorders) and psychiatric illness (depression, anxiety) have all been associated with ED.

A brief psychosocial assessment can be valuable given the interpersonal nature of sexual relations. Important elements of the assessment include past and present partner relationships, altered self esteem or coping ability, history of sexual trauma or abuse, and social and occupational role performance.

PBM Publication No. 99-0014 June 1999
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The physical exam may confirm findings of the history (presence of atherosclerosis) and occasionally reveal unexpected physical findings (penile curvature). The examination should emphasize the genito-urinary (penile, testicular, and rectal exam), neurolgic and vascular systems. Important findings include abnormal penile or testicular anatomy, prostate pathology, neuropathy/radiculopathy, occlusive or aneurysmal vascular disease or stigmata of endocrinologic illnesses (lack of secondary sexual characteristics, small testes).

Patient education is a necessary component for the successful treatment of ED. Education of the patient and partner should include information on the causes, misconceptions about ED, the treatments available for ED and their associated benefits and risks. Appendix 2 is a sample patient education tool for use by the providers with patients and partners.

Table of Evidence

Intervention Evidence	Reference	Strength of Recommendation	Level of
History and Physical Exam is an essential first step in the evaluation of ED	1	I	C
	2	I	C
	3	I	C

References

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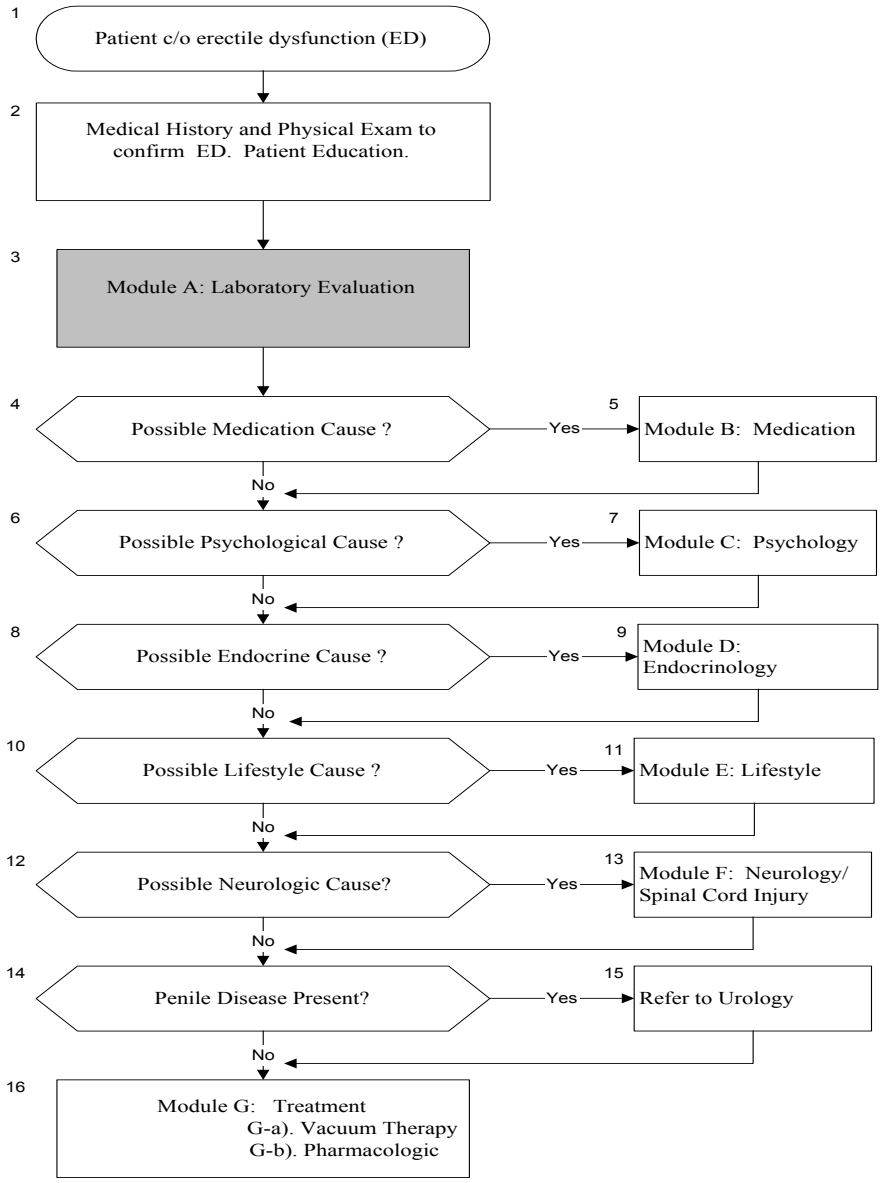
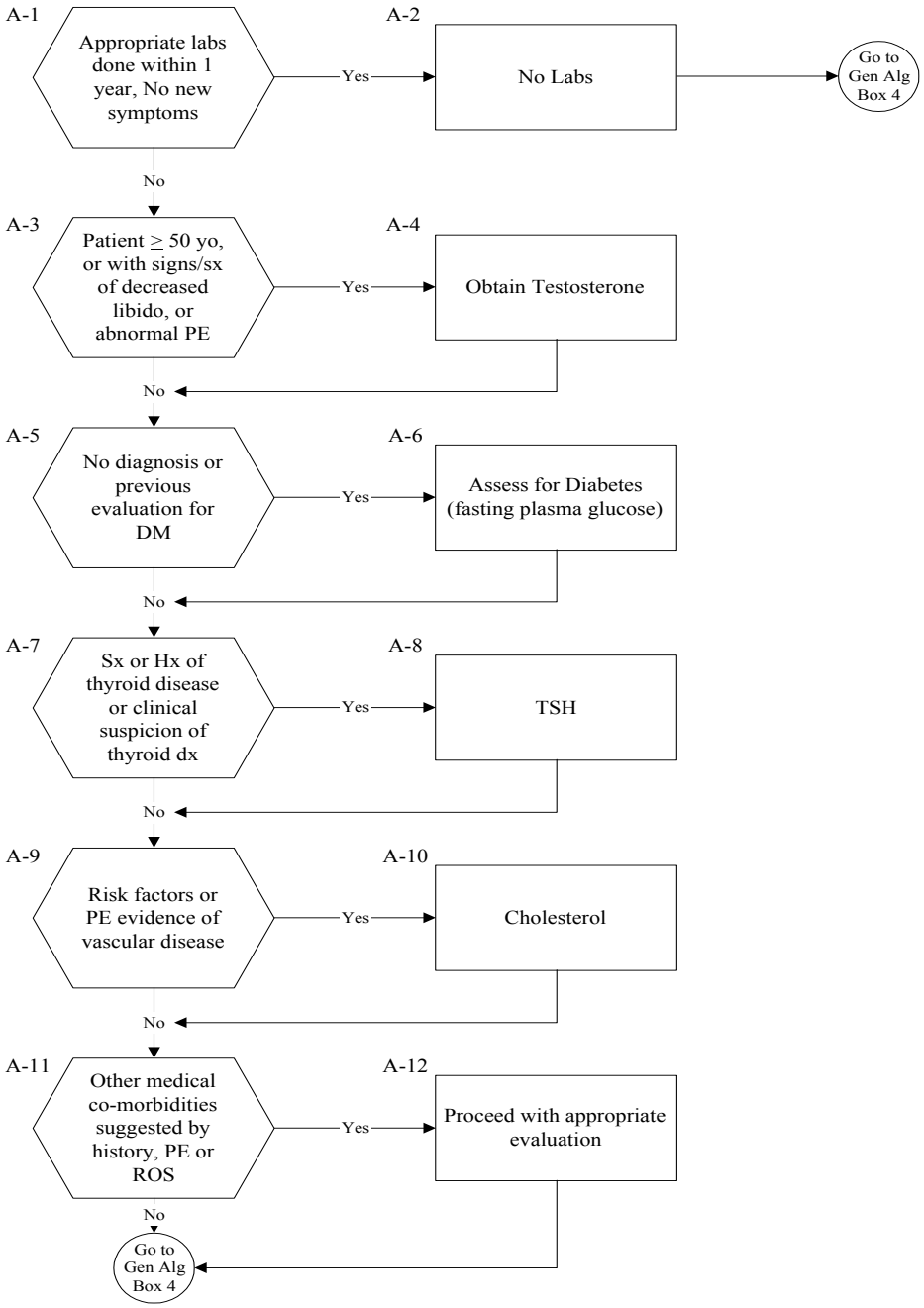
3. Sadovsky R, Dunn M, Grobe B, Erectile Dysfunction: The Primary Care Practioner's View. Am J Man Care 1999; 5(3): 333-341.

General Algorithm



Module A: Laboratory Evaluation of Erectile Dysfunction



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Module A: Laboratory Evaluation

Objective: To describe a rational approach to the laboratory evaluation of ED.

Summary: Erectile dysfunction (ED) may be related to undiagnosed medical disorders that if treated, may improve the patient's ED. Some patients presenting with ED may not have previously sought medical attention, and thus evaluation of ED offers an opportunity to diagnose and treat associated medical conditions. A rational approach is to do a laboratory evaluation that uncovers associated medical conditions and identifies treatable causes of ED.

Unfortunately, there is only limited evidence to recommend any specific laboratory panel to evaluate ED. Published suggestions vary from a minimal work up (10,12), to a moderate work-up (7, 8, 13), to an extensive laboratory evaluation (5,7,11). For example, the NIH Consensus Conference on Impotence recommends a moderate work up with measurement of testosterone in all patients, and serum prolactin, complete blood count, urinalysis, creatinine, fasting lipid profile, fasting blood sugar, and thyroid function testing in many patients.

In the absence of definitive evidence, selection of laboratory tests for the evaluation of ED can be based on the history, review of symptoms, and physical examination. The goal of selected laboratory testing is to identify important co-morbidities that warrant further evaluation or treatment, as well as help in the identification of the etiology and potential treatment for ED.

Discussion:

Testosterone: Testosterone should be measured in the morning, as there are diurnal variations in concentrations. Assessment of free testosterone or bioavailable testosterone is preferred, as total testosterone may be influenced by other medical conditions (12).

Although low testosterone may be associated with decreased libido, testosterone appears to have little direct effect on erectile function. Several investigators have examined the prevalence of hypogonadism in patients with erectile dysfunction, and found initial testosterone low in approximately 10% (1) and 15% (4) of patients. With repeated testing Govier determined that approximately 7% of patients had hypogonadism (4); Buvat found overall prevalence of low testosterone at 4% before age 50, and 9% for over 50 years. A history of decreased libido did not predict low testosterone (4).

Prolactin: Prolactin levels are not routinely necessary in patients with ED. Although rare, patients with pituitary tumors may present with ED. In several studies, overall incidence of prolactinoma is less than 1% (1). Therefore, in the absence of a clinical suspicion of this disorder, the cost of testing does not justify expense unless both testosterone and LH (Leutinizing Hormone) are low (see Endocrine Module D).

Laboratory Evaluation for Diabetes: Patients with no previous diagnosis of or recent evaluation for diabetes can be screened by obtaining a fasting plasma glucose.

Because the prevalence of ED is significant in diabetes, it is reasonable to assess patients who do not have a diagnosis of diabetes for this condition. In the Massachusetts male aging study 28% of men with diabetes had complete impotence (3). Thus, while treatment of diabetes will not improve symptoms of ED, it is important that a new diagnosis of diabetes is not missed.

Laboratory Evaluation for Thyroid Disease: Patients with a history or symptoms of thyroid disease, or patients where there is reasonable clinical suspicion for occult thyroid disease can be screened with a TSH (Thyroid Stimulating Hormone).

Both hyperthyroidism and hypothyroidism may rarely be associated with ED. While some authorities suggest screening of all patients for thyroid disease (7), a focused screening is more likely to be cost efficient. It should be noted that undiagnosed thyroid disease is not uncommon in the elderly, and the signs and symptoms in this population may be somewhat vague (such as weight loss or gain, fatigue, muscle weakness, depression, or confusion).

Laboratory Evaluation for Vascular Disease: Patients presenting with ED who have not been screened for hyperlipidemia can be screened with a fasting cholesterol or lipid profile.

As vascular disease is a common co-existing condition, patients who present with ED may have undiagnosed vascular disease. The laboratory evaluation is limited to assessment of lipid status. While treatment of hyperlipidemia will not resolve symptoms of ED, a diagnosis of elevated lipids and treatment may have other benefits for the patient.

Laboratory Evaluation of other Medical Comorbidities: During the history and physical examination of patients with a diagnosis of ED, other significant medical problems may be suggested, such as liver, renal, or prostate disease. As many patients may present for evaluation of ED without previous medical attention, there may be undiagnosed medical conditions that warrant further evaluation. Appropriate laboratory tests in these patients should be performed in addition to any specific laboratory testing done as part of the ED evaluation.

Table of Evidence

Intervention	Reference	Strength of Recommendation	Grade of Evidence
Testosterone in men ≥50 yo, decreased libido, or abnormal PE	1, 4	IIa	B
FBS in pts without history or diagnosis DM	7, 9	IIa	C
TSH for symptoms, suspicion of thyroid dz	7, 9	IIa	C
Screening Cholesterol	7, 9	IIa	C

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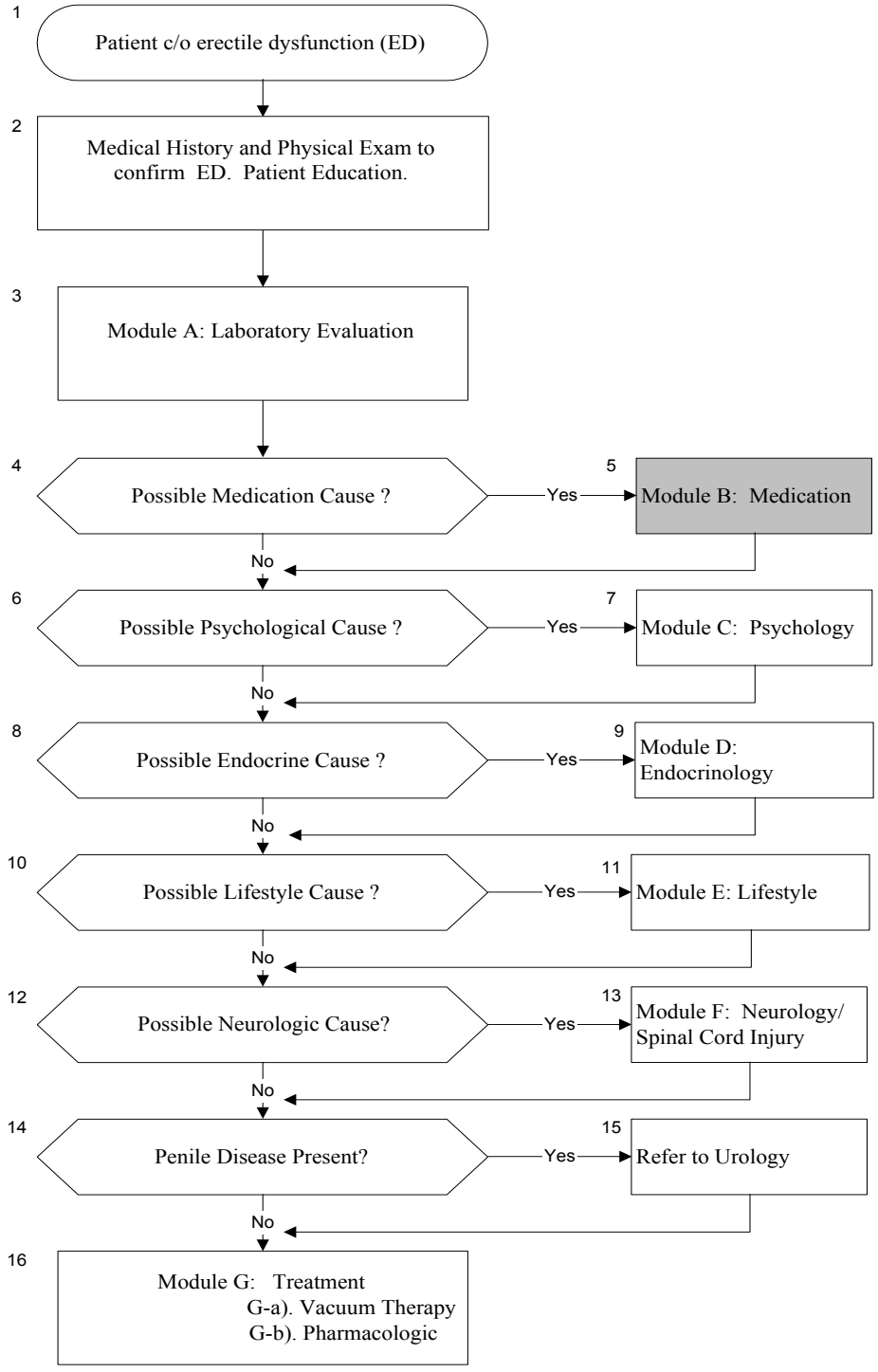
14. Wierman ME, Cassel CK. Erectile dysfunction: a multifaceted disorder. Hospital Practice 1998; 33: 65-74, 77-8, 83-9, 89-90.

General Algorithm



Module B: Medications

Objective: To identify medications which may contribute to a patient's erectile dysfunction.

Summary: Medications may be important contributors to ED (1-5). More than one drug may affect sexual functioning, or medications may be additive to other causes of ED. There may be a temporal relationship between onset of ED and institution of a new medication.

Discussion: Except in situations where institution of a medication coincides with onset of ED, it is unlikely that manipulating medications will completely restore erectile function. Thus, discontinuing medications that potentially cause ED should be carefully weighed against potential benefits of these drugs. Substitution between drug classes may improve sexual functioning (e.g., alpha blocker instead of beta blocker for hypertension). The risks and benefits of modifying the treatment regimen should be discussed with the patient.

Antidepressants – Consider substitution with Bupropion, Nefazodone, or Mirtazapine (6-7).

Antihypertensives – Erectile dysfunction may be seen with any drug that lowers blood pressure (14).

Antipsychotics – Commonly used agents phenothiazine and haloperidol may have CNS effects and/or hormonal effects on sexual function. The use of olanzapine, instead of traditional antipsychotics, may be helpful as it causes less elevation of serum prolactin levels (15,16).

Nicotine – Nicotine produces both acute (9-10) and chronic (11-12) effects on erectile function.

SSRI's – Assess for impaired ejaculation and anorgasmia (7), which may be perceived by patients as erectile dysfunction. If not possible to remove, substitute or reduce the dose of the medication, consider buproprion "augmentation" (1-2 hrs. prior to intercourse prn or scheduled) (8).

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Module B: Medication With Potential Effects On Erectile Function

MEDICATIONS	CATEGORY
Alcohol	CNS
Androgens	H
Antiandrogens (flutamide, nilutamide, bicalutamide)	H
Antiarrhythmics	CV
Anticholinergics	CNS
Anticonvulsants	CNS
Antidepressants, MAOI, SSRI, Tri/Heterocyclics	CNS
Antihistamines, anticholinergic*	CNS
Antineoplastic/cytotoxic drugs	H
Benzodiaziepines	CNS
Adrenergic blockers (alpha & beta)	H, CV
Central Alpha-2 Adrenergic Agonists	CV
Cimetidine	H
Clofibrate	CV
Decongestants (alpha-adrenergic agonists)	CNS
Digoxin	H, CV
Diuretics-Carbonic anhydrase inhibitors	CV
Diuretics-Thiazide	CV
Estrogens, conjugated estrogens	H
Ethanol	H
Finasteride	H
Gemfibrozil	CV
Glucocorticoids-systemic	H
Haloperidol	H, CNS
Ketoconazole	H
LHRH Agonists (goserelin, leuprolide)	H
Lithium	CNS
Marijuana	H, CNS
Megestrol	H
Methydopa	H, CV
Metoclopramide	H
Nicotine	CNS, CV
Opiates	H, CNS, CV
Phenothiazines	H, CNS
Reserpine	H, CV
Spironolactone	H, CV
Tetracycline	H

KEY: **CV** = Drugs associated with CARDIOVASCULAR EFFECTS on Sexual Function
CNS = Drugs associated with CENTRAL NERVOUS EFFECTS on Sexual Function
H = Drugs associated with adverse HORMONAL EFFECTS on Sexual Function

* Anticholinergic antihistamines & decongestants are combination ingredients in many of OTC (over the counter, non-prescription) & legend (Rx) cough, cold, & allergy products (brand/generic).

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Table of Evidence

Intervention	Reference	Strength of Recommendation	Level of Evidence
Consider substitution of SSRI with bupropion, nefazodone, or mirtazapine	6 7	II a II a	C C
Consider bupropion "augmentation" if not possible to remove/substitute or reduce dose of SSRI	8	II a	B
Consider alpha blockers, ACE Inhibitors, or Calcium Channel Blockers as alternative antihypertensive treatment	1 2 5 10	II a II a II a II a	C C C C
Assess for impaired ejaculation or anorgasmia	7	I	C

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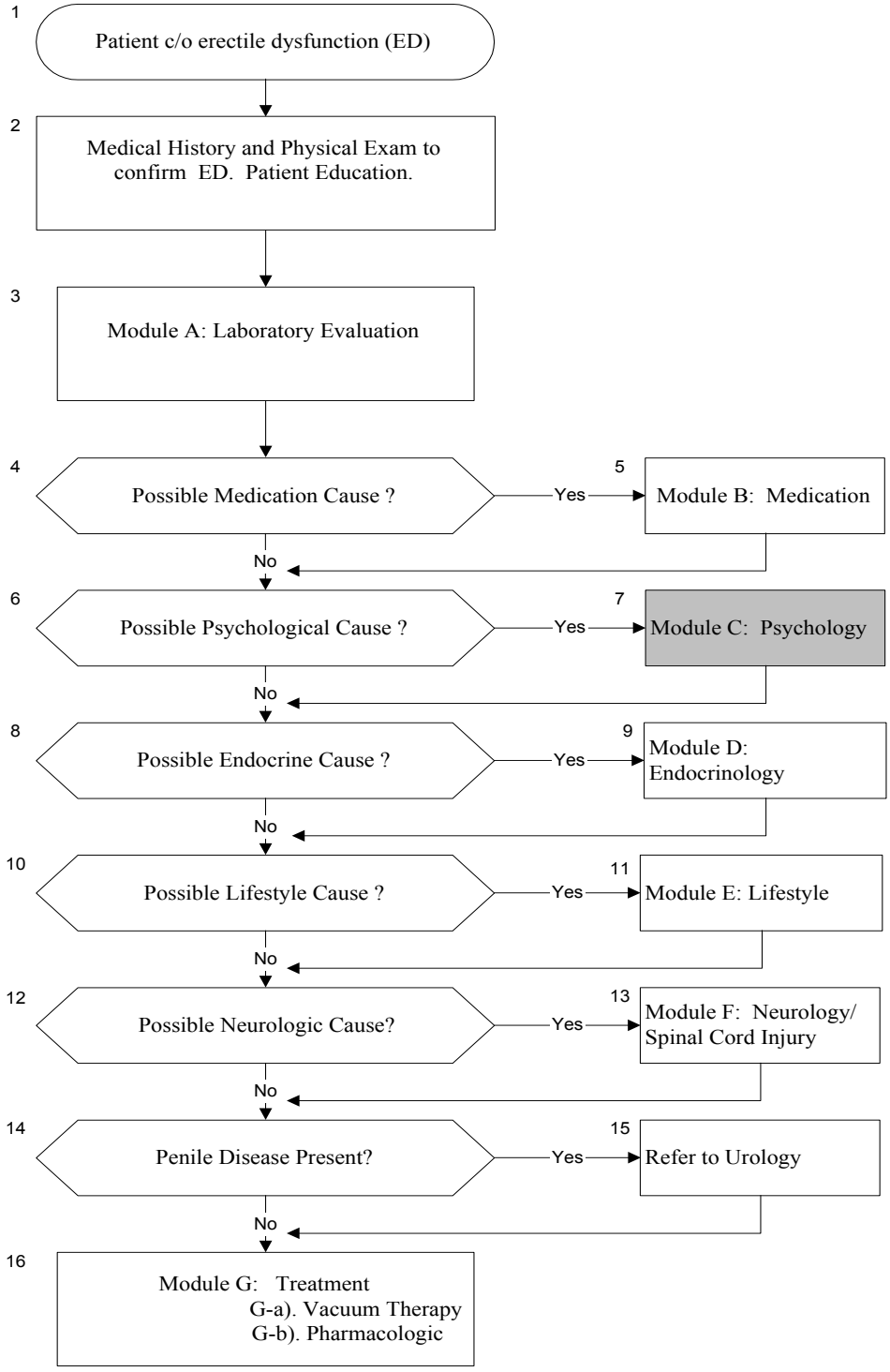

Module C: Psychology

Psychological Factors and Referral Considerations in Assessment and Treatment of Erectile Dysfunction (ED)

Objective: To describe the process of evaluating and treating psychological factors associated with ED and clarify when a referral to a sex therapist or appropriate Mental Health Professional is indicated related to these risk factors.

Summary: The patient may be referred for sex therapy assessment when there is concern the patient is clinically depressed, has a sexual trauma history, experiences anxiety and/or guilt regarding sex or reports conflict with their partner (2,8,10,11). Findings from further evaluation of these risk factors may lead to an array of psychosexual interventions designed to achieve symptom relief and allow the patient to enjoy their optimal level of sexual health. It is important to note that ED typically has a multicausal basis and that concurrent, brief sex therapy may be beneficial to patients employing medical treatments for their ED (2,8,11).

Discussion: There are six questions useful to primary care providers related to screening patients for psychological risk factors for ED. Positive responses to either of the first two questions should dictate referral and/or further evaluation. These questions are:

Q1. Do you have naturally occurring erections in the morning or can you get an erection with yourself (by masturbation)?

Q2. Have you ever been sexually molested or sexually assaulted, either as a child or an adult?

The last four questions are answered on the following four point scale: 0 = no, not at all; 1 = yes, seldomly; 2 = yes, quite a bit; 3 = yes, frequently. An answer of "2" or "3" on any of these four questions indicate referral and/or further evaluation. These four questions are:

Q3. Do you feel depressed?

Q4. Do you feel nervous or anxious regarding sex?

Q5. Do you feel guilty regarding sex?

Q6. Do you have significant conflict with your partner regarding sex?

A comprehensive assessment of ED requires an in-depth sexual development history be completed on each patient (2,8,10,11). Since the patient's complaint of ED may be a symptom of depression (1,13), a standardized screening for depression is recommended, such as the PRIME-MD or Beck Depression Inventory (BDI). BDI scores of 20+ indicate a moderate to severe level of depression and that treatment is indicated (3). Care should be taken in the selection of antidepressants to avoid exacerbation of erectile dysfunction (11).

If the patient has a sexual abuse history, a referral to a sex therapist will ensure a sensitive and careful evaluation of the trauma nature and severity. A sexual dysfunction may be a long-term sequela of sexual trauma (4,9), however sexual trauma, by itself, may not be related to the presenting complaint of ED and may not require psychotherapy.

More commonly, anxiety or guilt may serve as a psychogenic obstacle to erectile response. These etiological factors can be effectively treated through relaxation training, cognitive therapy, and behavioral prescriptions (6,10). If significant relationship conflict exists, it needs to be resolved at least to a point where the couple mutually desires physical intimacy (6,10). Couple counseling focusing upon conflict resolution is indicated.

Sex therapy represents the combination of psychotherapy and prescribed behavioral exercises which focus upon relaxation and skill acquisition related to sensual touch. Between talk therapy sessions, behavioral assignments are completed within the couple's own value system and the privacy of their own home. These behavioral prescriptions are referred to as "sensate focus" exercises and their effectiveness has been extensively studied (5,6,10).

Overall efficacy of sex therapy (Masters and Johnson model) is 82% across all sexual dysfunction but falls to 80% success rate for psychogenic secondary-type ED and 68% success rate for primary-type ED (10). Couples often benefit from brief sex therapy during their concurrent use of medical treatments for ED (2,8,11). Couples that refuse these treatment options need to be re-evaluated for alternative interventions.

Table of Evidence

Intervention	Reference	Strength of Recommendation	Level of Evidence
Patients with ED and naturally occurring erections (a.m. or masturbation) are referred for sex therapy	2	1	C
	8	1	C
Patients without an organic-based ED but with depression, guilt, anxiety, sexual abuse hx or high relationship conflict are referred for sex therapy	11	1	C
	10	1	B

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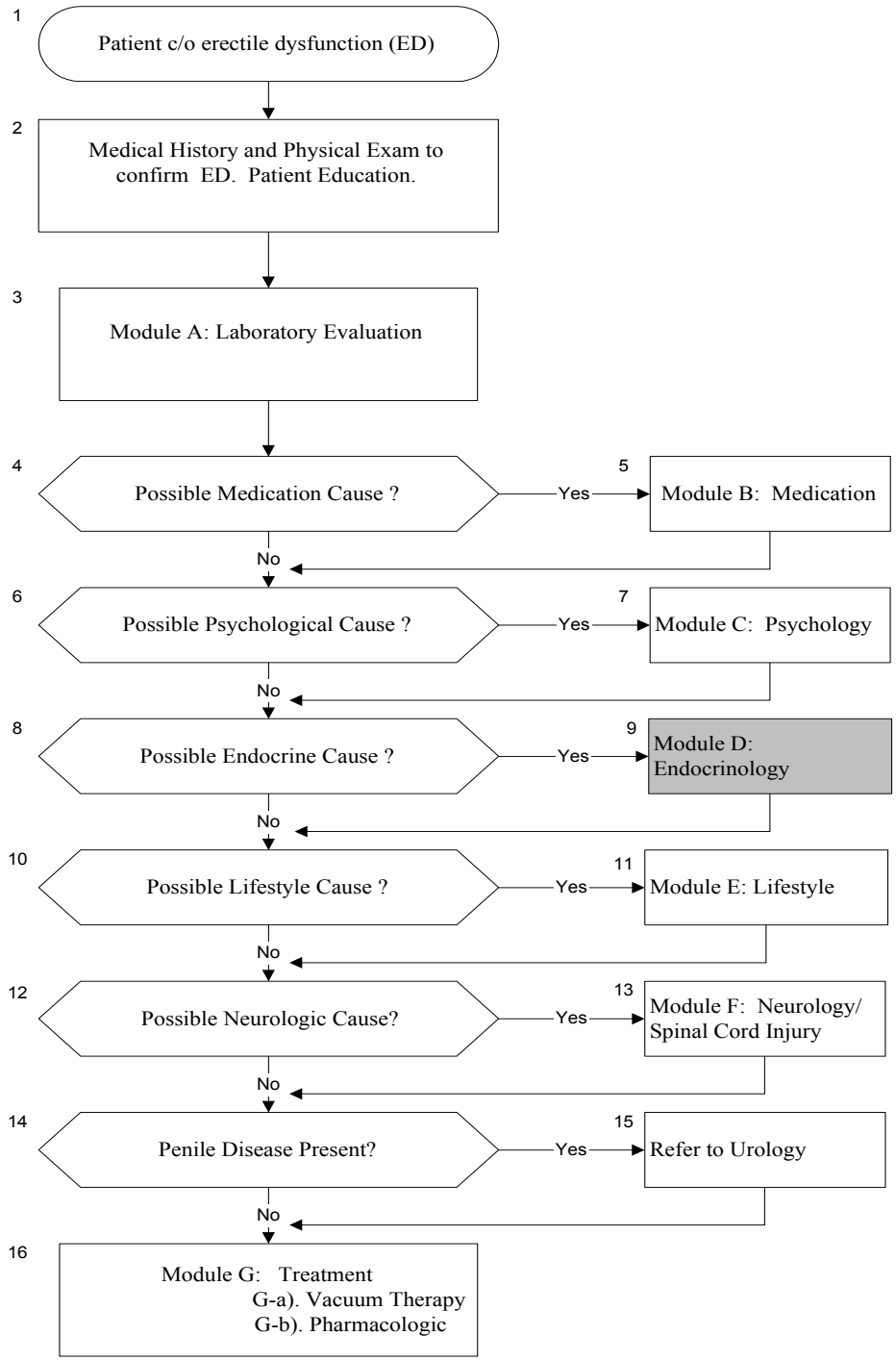
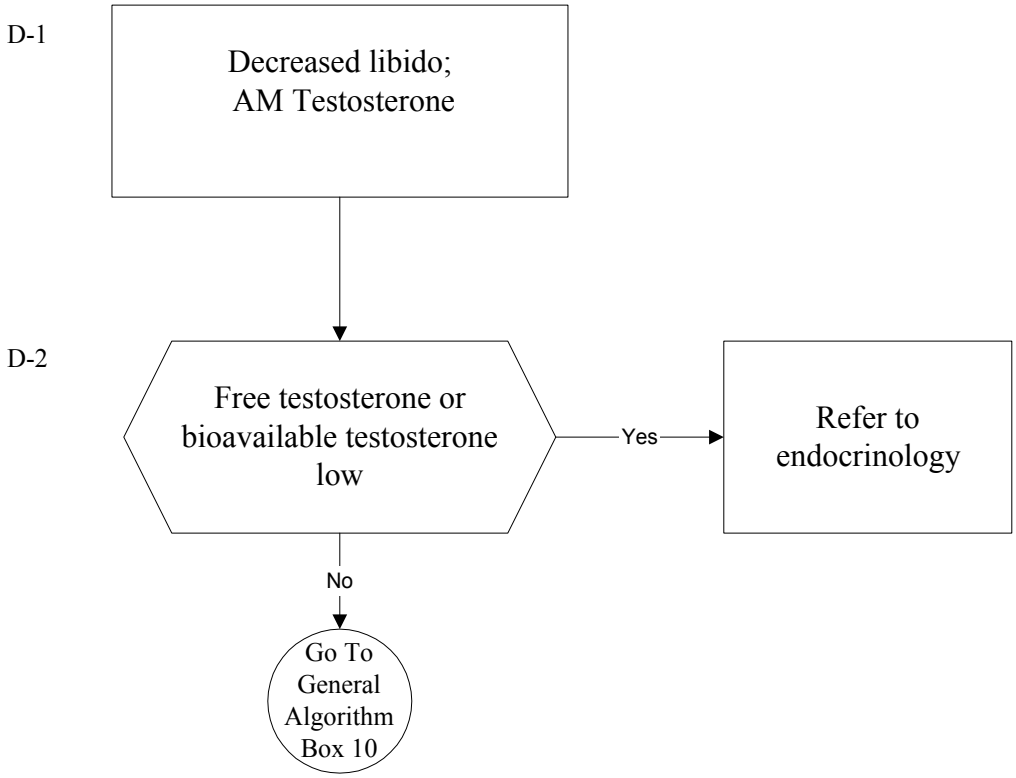


Module D: Endocrinology



Module D: Endocrinology

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Objective: To describe the endocrine etiologies and evaluation in patients with erectile dysfunction.

Summary: The two most common endocrine etiologies for ED are testosterone deficiency and diabetes mellitus. In patients with ED and decreased libido a free or unbound testosterone should be obtained. If this is abnormal (see discussion) the patient should be referred to endocrinology for confirmation of the diagnosis of hypogonadism and for evaluation of the etiology. Other endocrine disorders only rarely present with a principal complaint of ED. Thus other endocrine tests are not warranted without specific symptoms and signs of specific endocrine disorders.

Discussion: Gonadal Hormones.

Testosterone does not appear to have a direct effect on erectile function in humans. However, testosterone does influence libido, which in turn may alter erectile function. (1) Measurement of free or unbound testosterone is preferred since these are not influenced by primary changes in testosterone binding proteins. Blood should be obtained in early AM since there is diurnal variation in younger males. There is a significant decrease in testosterone with aging. Whether this decrease is "normal" and should be taken into account in reference values is controversial. (2). If age adjustment is not used there may be some degree of over-diagnosis in the elderly and under-diagnosis in younger patients.

Once testosterone deficiency is documented the next step in the evaluation is to determine whether the abnormality is testicular (primary hypogonadism) or hypothalamic-pituitary (secondary hypogonadism) in origin. Finally, the specific etiology, particularly for those individuals with secondary hypogonadism, must be determined.

In the absence of contraindications low testosterone should be treated with one of several available forms of testosterone. This treatment may have a major effect or no effect on erectile function. Irrespective of this response on erectile dysfunction testosterone replacement therapy should be continued due to its positive effects on bone, muscle, and lipid metabolism. An endocrinologist should do these additional evaluations and initiate the treatment of male hypogonadism.

Discussion: Diabetes Mellitus.

Diabetes is one of the most frequent organic causes of ED. Diabetes may cause ED through diabetic autonomic neuropathy, diabetic microvascular disease, or peripheral macrovascular disease. (3) These complications develop over a number of years. Thus ED is only rarely the presenting complaint for the diagnosis of diabetes.

Controlling glucose is a major goal in all diabetics and in many instances delays or prevents the development of these complications. However, once these complications, including ED occur

then achieving or maintaining glucose control is unlikely to reverse the ED. At this time there are no specific treatments available for diabetic autonomic neuropathy.

Discussion: Other Endocrine Disorders.

Rarely excess or deficient concentrations of thyroid hormone or cortisol may cause ED. Testing for these endocrinopathies does not need to be done unless more specific symptoms and signs of excess/deficiency are present.

Table of Evidence

Intervention	References	Strength of Recommendation	Grade of Evidence
Measurement of free testosterone	1,2	IIA	C
Age adjustment of free testosterone	1,2	IIb	C
ED virtually never the presenting Sx of DM	1-3	I	C
Other endocrine tests not necessary	1,2	I	C

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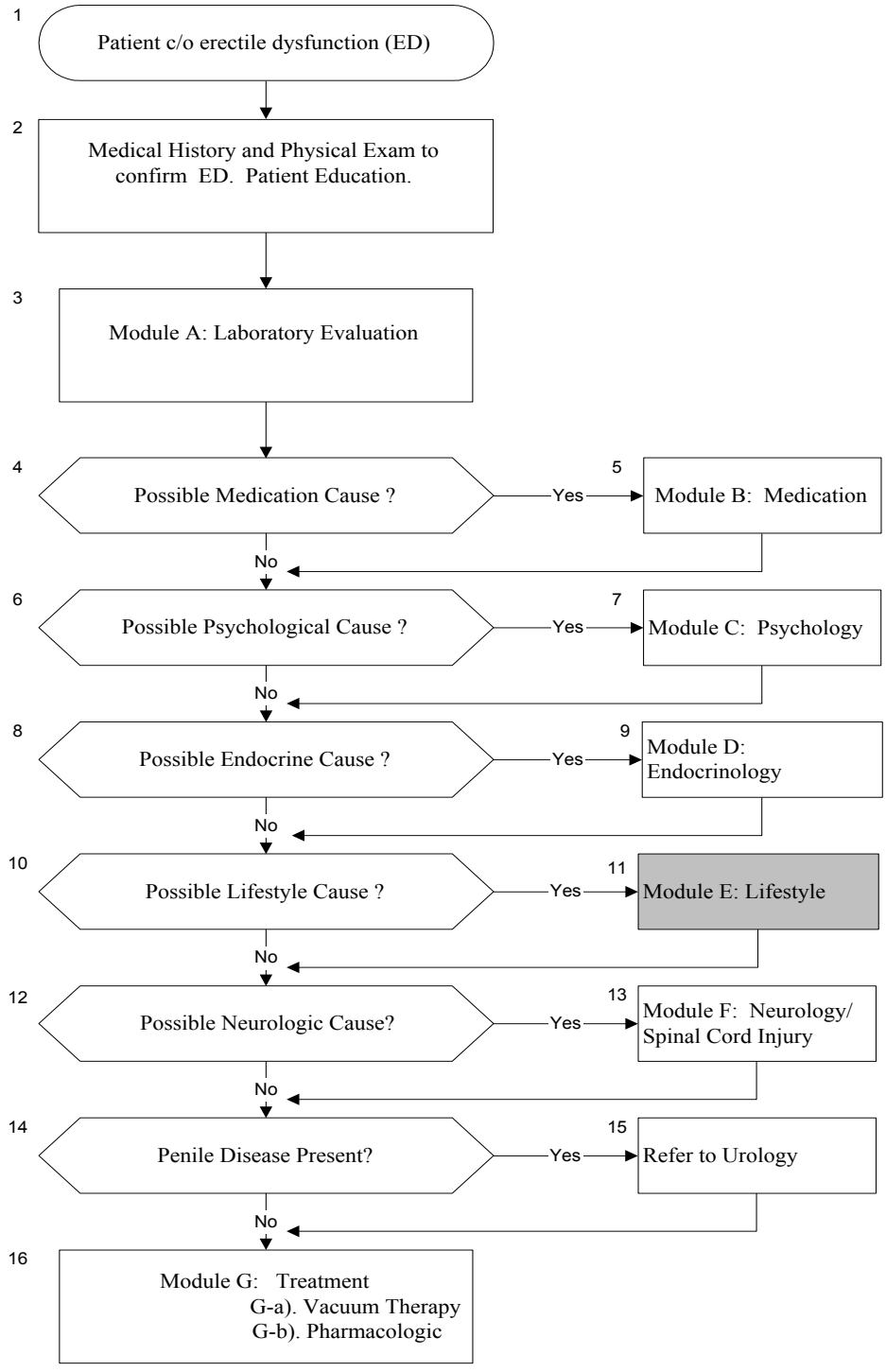
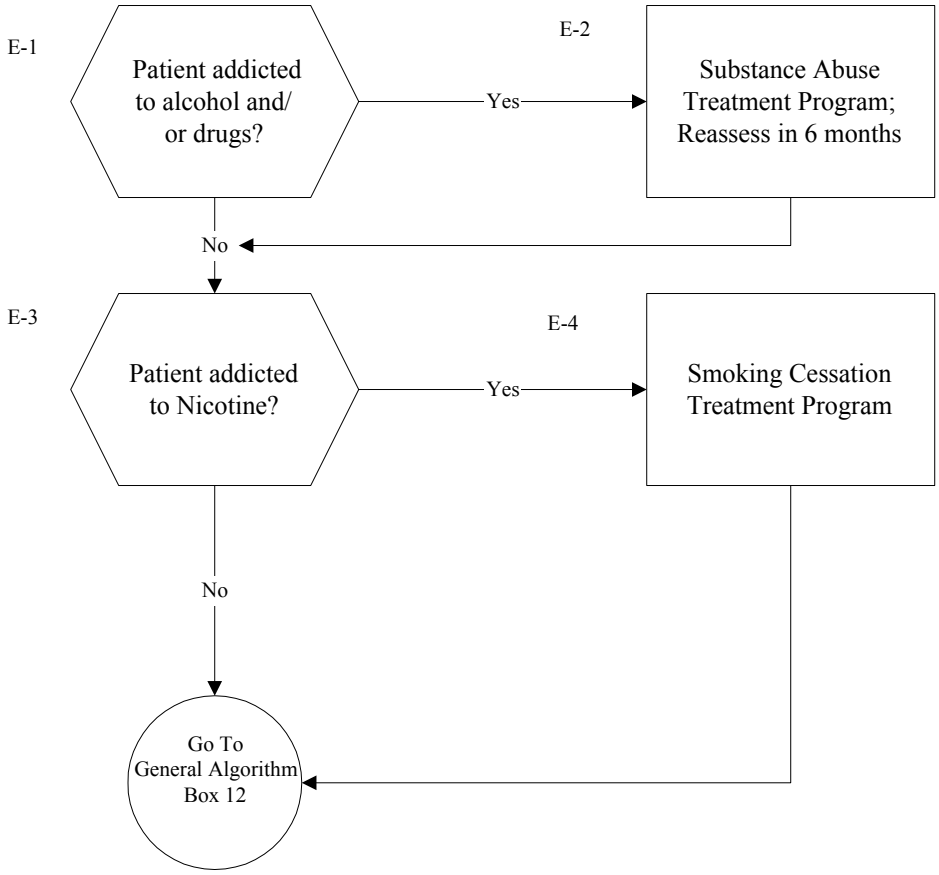


Module E: Lifestyle



Module E: Lifestyle

Objective: To describe the process of evaluating and treating lifestyle factors associated with ED and clarify when a referral is indicated related to these risk factors.

Summary of Annotation: The patient may be referred for specialty assessment and treatment when there is concern the patient has an addiction to alcohol, tobacco or illegal drugs which have adverse effects on erectile functioning. All patients who are smoking should be referred to a smoking cessation program if cessation efforts fail in the primary care setting (1, 5, 7). Patients with addictions to alcohol and/or drugs should be referred for further assessment and treatment by a polysubstance abuse program (1, 5, 7). It is important to note that ED typically has a multicausal basis and concurrent combination of therapies may improve treatment outcome (1, 5).

Discussion: A comprehensive assessment of ED includes an in depth sexual development history be completed on each patient (1, 5, 7). Addictions to substances, whether legal addictions (alcohol and tobacco) or illegal addictions (amphetamines, cocaine, heroin, marijuana, morphine or steroids) represent risk factors for ED (3, 4, 6, 8).

There are four questions useful for primary care providers related to screening patients for addictions as risk factors associated with ED. These questions are referred to as the "CAGE" assessment and are most often used to differentiate between social drinking and alcoholism.

Q1. **C**-Have you thought that you should "CUT" down on your alcohol (or drug) use lately?

Q2. **A**-Have you been "ANNOYED" recently about being criticized for your alcohol (or drug) use?

Q3. **G**-Have you felt "GUILTY" about your alcohol (or drug) use?

Q4. **E**-Do you need an "EYE OPENER" in the morning by using alcohol (or drugs) to get going?

An affirmative response to two of the four questions indicates referral to Alcohol Anonymous (AA) and/or an addiction treatment program. It is important to note that patients commonly minimize their alcohol/drug use during assessment.

If the patient has an addiction to alcohol only, then a referral to an alcohol abuse treatment program and active participation in AA would be indicated. Most frequently, patients have coexisting addictions to alcohol and drugs. Often, the only addiction treatment program available is a polysubstance abuse program and then the referral reflects this practical reality regardless of the drug of choice. The referral to a polysubstance abuse treatment program and/or AA would be appropriate with reevaluation of ED in six months (3, 4, 6).

As tobacco use is a significant risk factor for ED, all patients should be assessed for their use of tobacco products (not just cigarettes). The VHA/DoD Clinical Practice Guidelines to Promote Tobacco Use Cessation in the Primary Care Setting (which are based on the AHCPR clinical practice guidelines on smoking cessation) should be followed for assessment and counseling patients by primary care providers (2, 10). Patients failing at cessation in primary care settings should be offered referral to a specialized smoking cessation program employing the AHCPR guidelines, which incorporate behavioral, educational and nicotine replacement therapies.

Questions sometimes arise with providers and patients as to the "staging of treatment" or which addiction should be treated first and if treatment of ED should proceed if addictive behaviors continue. Generally, treatment of addictions to illegal drugs are prioritized over treatment of legal addictions. As often is the case, if a patient is addicted to alcohol and illicit drugs, treatment for these addictions should be prioritized over smoking cessation. Patients often report that it is more difficult to give up smoking than overcoming their addictions to alcohol or illicit drugs. Concurrent treatment of drug, alcohol and nicotine addictions is not recommended unless the patient participates in a highly structured, inpatient or residential program.

Table of Evidence

Intervention	References	Strength of Recommendation	Level of Evidence
Patients who use and have dependence upon alcohol, tobacco or illegal drugs (amphetamines, cocaine, heroin, marijuana, morphine, steroids) should stop their use of	4	I	C
these substances via counseling from their doctor and/or participation in a specialized tx program	2	I	C
	6	I	C

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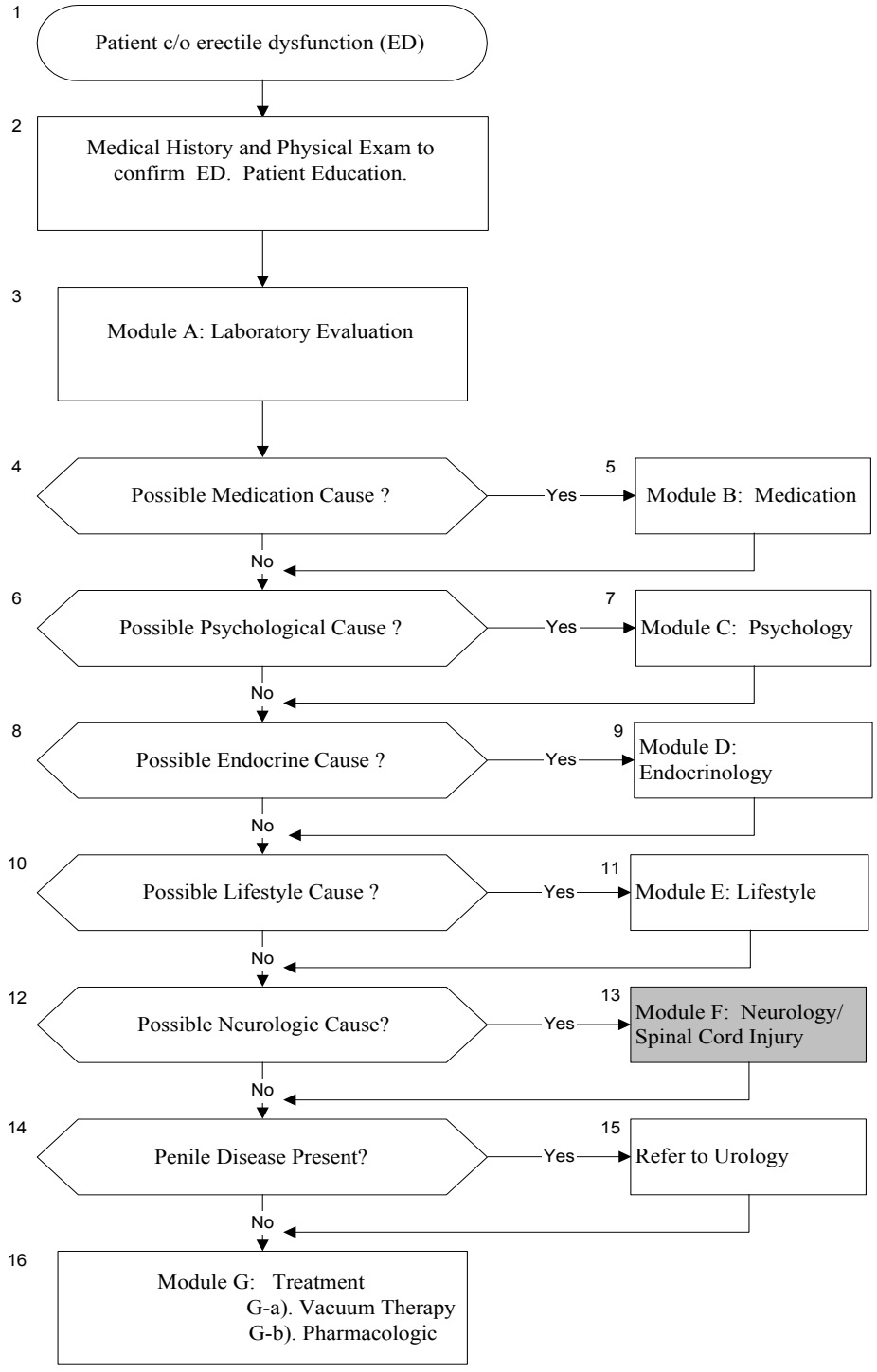
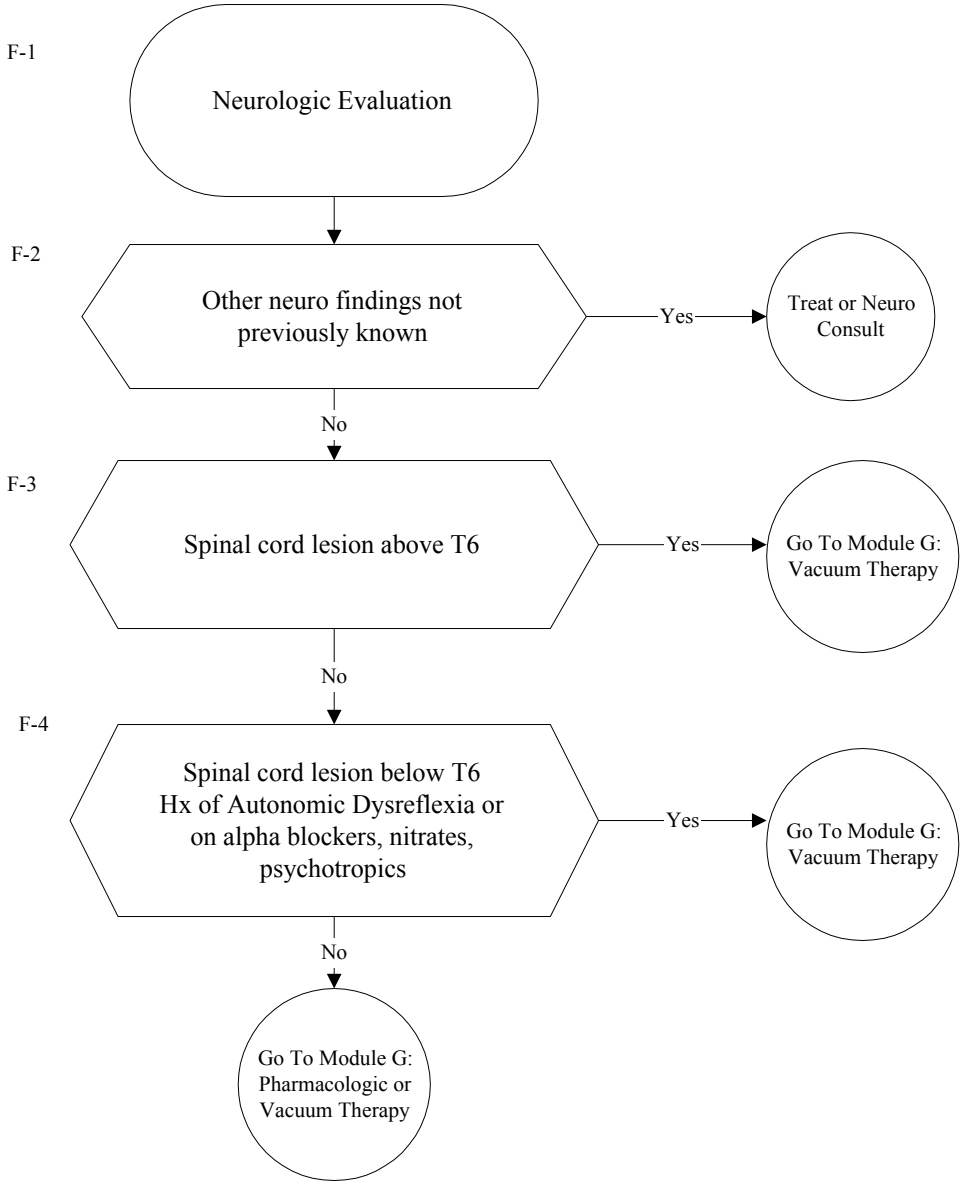


Module F: Neurology/Spinal Cord Injury



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Module F: Neurology/Spinal Cord Injury

Objective: To describe the evaluation and the treatment of patients with erectile dysfunction due to spinal cord injury and other neurologic conditions.

Summary: Spinal cord injury (SCI) persons usually have a reflex erection particularly when physically stimulated. This is possible in all supraconal (above S2,3,4) lesions. Lesions of the conus and/or cauda equine result in lack or absence of erection on physical stimulation. In addition to spinal cord lesions, a wide variety of diseases of the Central and Peripheral Nervous System can result in erectile dysfunction. Hence a careful neurologic exam is necessary to exclude or identify such illnesses. Neuro-urologic examination and Urodynamics can help diagnose neurologic deficit which will impair bladder function and associated erectile dysfunction. In a recent randomized pilot study of 27 patients with below T5-6 lesion, 65% of the subjects had erections with improved rigidity at the base of the penis with sildenafil. However, responses to the end of treatment questionnaire, indicated that there were no significant differences between the placebo group and the sildenafil group with respect to frequency of erections hard enough for sexual intercourse (1). The patients with lesions above T5-6 are prone to autonomic dysreflexia (2,3,4). This being a life-threatening situation with sudden rise in blood pressure, they may be given nitrites for emergency management of hypertension and are therefore at risk with sildenafil for severe hypotension. It is important to appreciate that the usual systolic blood pressure of quadriplegics and high tetraplegics may be below 100 mmHg. Other options for the management of ED in these patients include penile implants preferably "semi rigid" which can also help to hold external condom drainage more easily in obese patients with small retractile penis. Other options include vacuum pump devices, intraurethral insertion of alprostadil (MUSE), and intracavernous injections of prostaglandins to manage erectile dysfunction.

Table of Evidence

Intervention/ Condition	References	Strength of Recommendation	Level of Evidence
Sildenafil 50 mg (Patient below T5-T6 lesions)	1	IIb	B
Autonomic Dysreflexia	2, 3	I	C
Penile Implants	4	IIa	C

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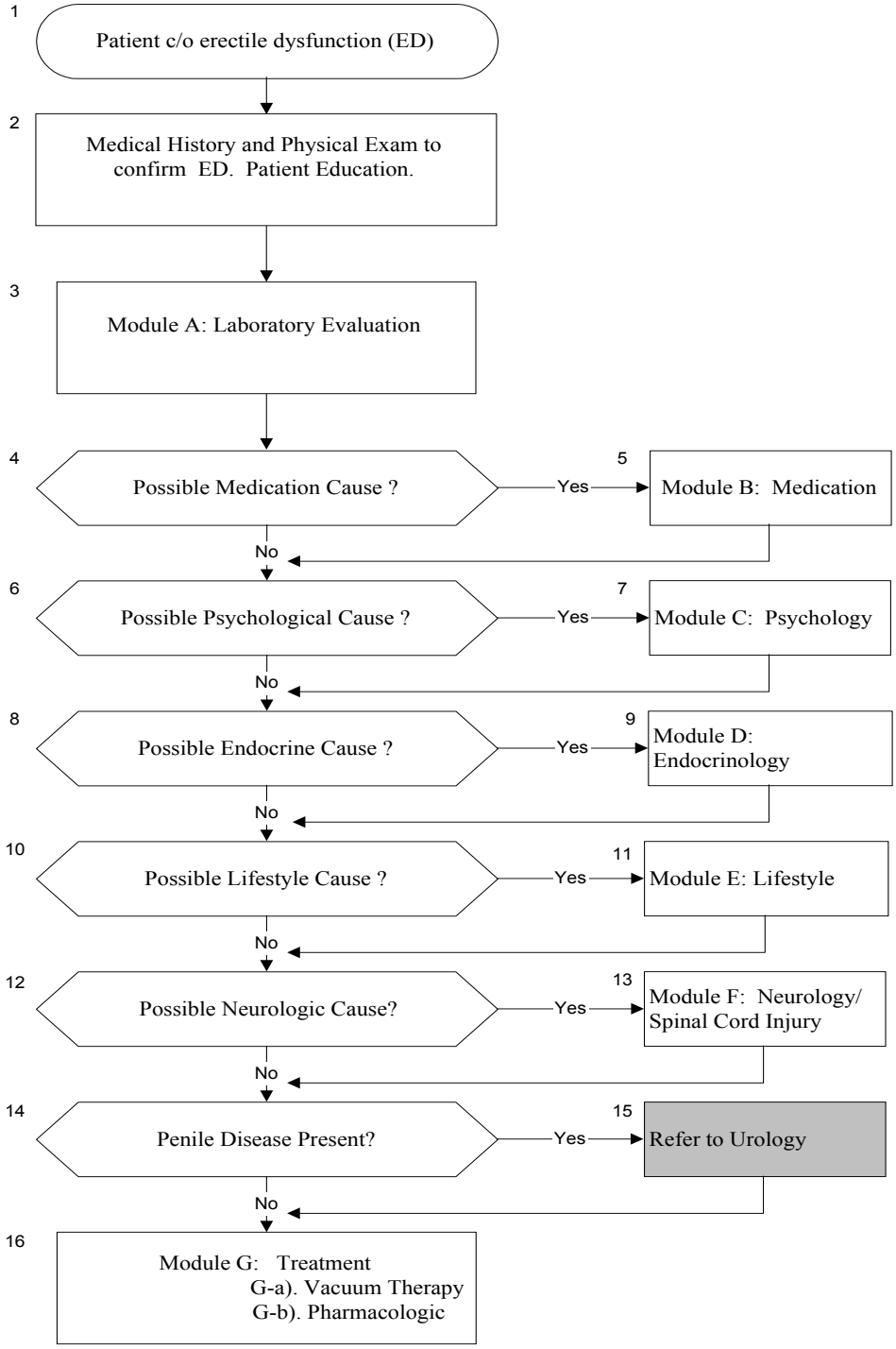

Boxes 14 and 15: Penile Disease Present? Refer to Urology

Objectives: To guide primary care providers (PCP) in the appropriate referral of erectile patients for urological consultation.

Summary:

1. Distinction between urological and non-urological causes of erectile dysfunction should be established by PCP for the appropriate management decision and referral for urological consultation.
2. Significant numbers of patients with erectile dysfunction have non-urological etiologies and can be managed by PCP and specialties other than urology. Patients should receive education on the various treatment options for ED; PCP can provide initial therapeutic choices such as vacuum erection device or oral medication.
3. When there is a lack of a successful response to initial therapy and/or presence of certain urological conditions (discussed below), urology referral is the appropriate next step.

Discussion:

Erectile dysfunction (ED) is a common medical condition of multiple etiologies, both urologic and non-urologic. Generally, ED is perceived as a urologic problem despite the fact that a significant number of patients have underlying non-urologic etiologies. A recent study reported that up to 17% of male patients experienced lack of interest in sex, 10% disclosed that sex was not pleasurable, and 32% had premature climax (1). In the same study, only 9-18% patients (percentage varied with age) had trouble maintaining or achieving an erection. A large population of patients actually suffer from sexual dysfunction, which is not directly related to penile disease or a urologic cause.

Distinguishing between the various causes of sexual dysfunction and erectile dysfunction is important in the decision to refer patients for urological consultation (2). Patients with "urological type" erectile dysfunction, i.e., with no psychogenic or other potentially reversible etiology, may be referred for urological consultation only after failure to achieve satisfactory results with first line treatment options (vacuum erection device and/or oral mediations). Other treatment options include intraurethral suppositories ("MUSE"), intracavernosal injection therapy and penile prosthesis. Penile prosthesis is considered last line therapy but may be appropriate in highly selected cases. Urologic consultation should be sought for patients with history of penile diseases such as Peyronie's disease, external genitalia trauma, penile or pelvic surgery, neurological disorders such as spine injury/surgery, and/or pelvic radiation therapy. Perineal trauma from bicycle seats is a reversible cause of erectile dysfunction.

Careful evaluation of patients before referral to urology will ensure efficient use of this specialty. Conflicting information on history should alert the provider to the possibility of psychological etiology. Such circumstances include patients claiming erectile dysfunction but are capable of achieving normal erection on waking up, during masturbation, with selective partners, or under certain circumstances. Stress and anxiety are also important in this psychological profile (2).

Other physical limitations may limit treatment options. For example, intracorporal injection therapy may be unsuitable in patients with inadequate hand dexterity such as in arthritis, visual impairment such as in diabetic retinopathy, or difficulty gaining sufficient access to the penis such as in obesity. Such awareness by the primary care providers may influence his/her decision when referring patients for urological consultation.

References

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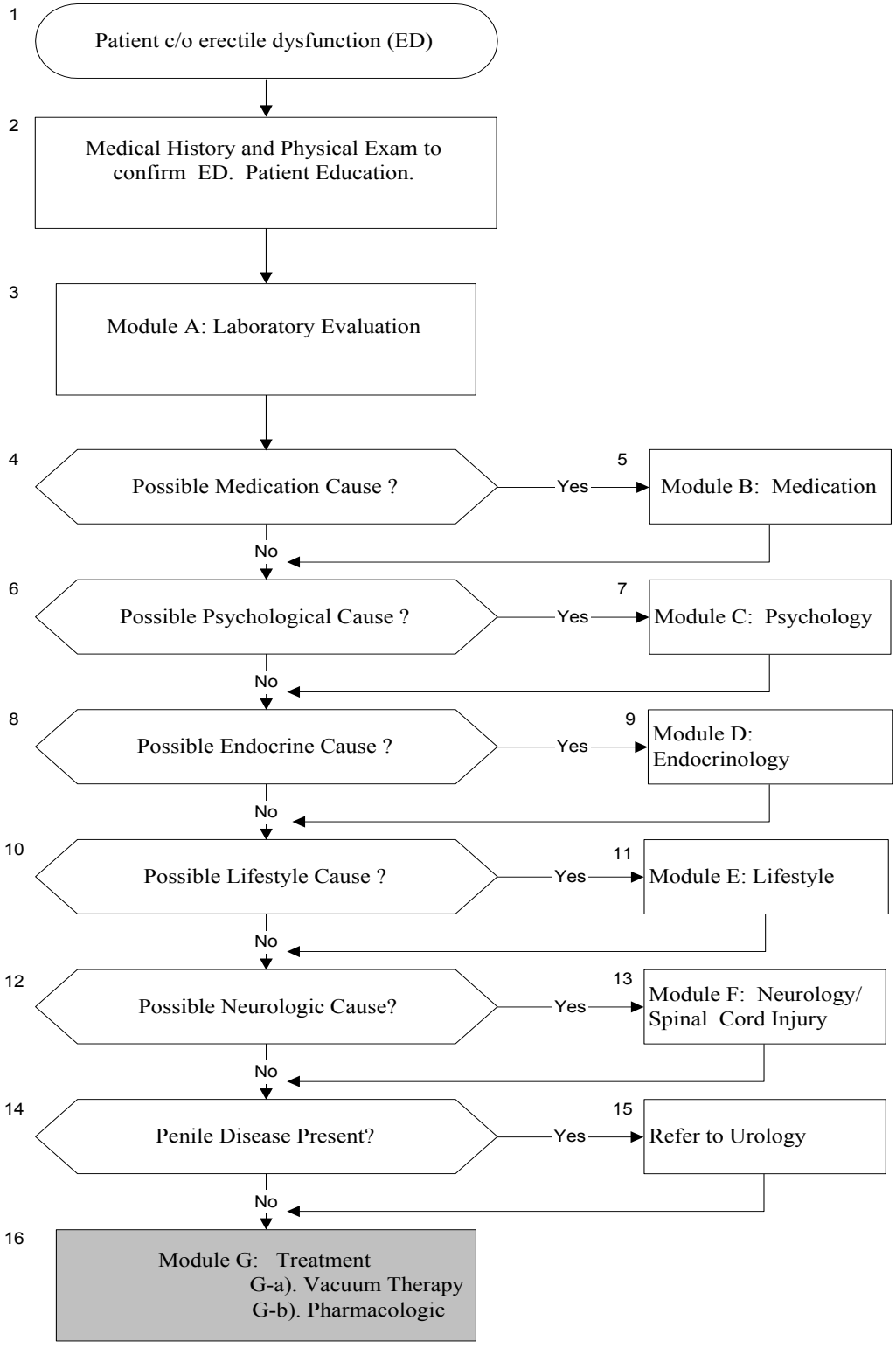
General Algorithm



Module G: Treatment

General Principals of Therapy

Secondary causes of ED should be eliminated prior to instituting other therapies wherever possible. Since ED is frequently multi-factorial, correcting some etiologies may not resolve the ED. Furthermore; some secondary causes may not be correctable (i.e. it may not be possible to use an alternative medication). The various treatment options and their advantages/disadvantages should then be discussed with the patient and partner/spouse. Of the total available treatments the following two are most appropriate initial therapies to be prescribed by primary care physicians (eg. Vacuum device, sildenafil).

Treatment Table

A. Non-Pharmacologic
1. Vacuum devices
2. Constriction devices

B. Pharmacologic
1. Oral Therapy
   a. sildenafil (Viagra)
   b. yohimbine
2. Urethral Suppositories
3. Intracavernosal Injections
   a. alprostadil (MUSE)
   b. papaverine
   c. multiple drug
4. Topical

C. Surgical
1. Penile Prosthesis
2. Penile Reconstruction for anatomic abnormalities
3. Vascular Reconstruction

D. Psychological Counseling/Sex Therapy
1. Sex Therapy
2. Relationship Counseling

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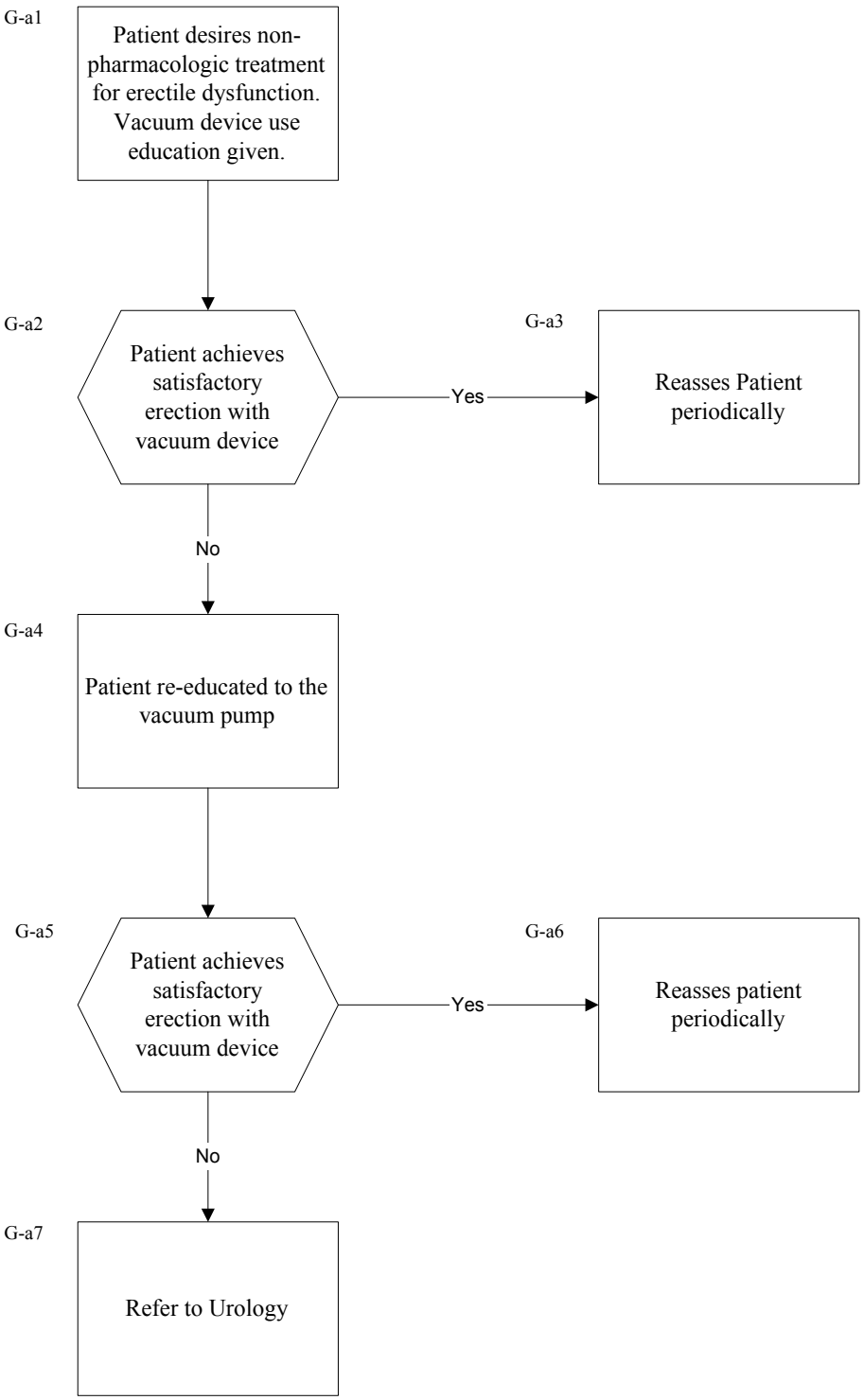
Module G: Treatment
a: Vacuum Therapy



Module G-a: Vacuum Pump Therapy for Erectile Dysfunction

Objective: To describe the process of evaluating and treating Erectile Dysfunction with vacuum pump therapy.

Summary: A non-pharmacological/non-surgical approach in the treatment of ED should always be considered as a first-line treatment modality (1). Vacuum pump therapy has no drug interactions and side effects are minimal. The occurrence of ED associated with such co-morbidities such as diabetes, hypertension, athlerosclerosis, autonomic neuropathy, drug effects, hypogonadism, and other major medical problems lends the potential for drug-drug interactions when a pharmacological approach is used for treatment.

Multiple studies have been done over the last several years, which clearly document the effectiveness of a vacuum tumescence device in varied groups of patients. Patient satisfaction with motivated subjects and partners is substantial.

The successful utilization of a vacuum tumescence device depends on appropriate patient education and counseling (2). Compliance and acceptance of therapy have been shown to be dependent on individualized instruction, return demonstration, and evaluation of decreased effectiveness with re-education by a fully trained, qualified instructor in a private setting. Qualified instructors may include urologists, physician extenders, nurse specialists, or certified manufacturer representatives. Patient education may also include the sexual partner to help increase successful utilization and satisfaction with the device. The use of written materials, videotapes (available from the supplier), and self-demonstrations are extremely valuable in achieving adequate patient education with the use of the device. Most patient dissatisfaction results from inadequate education and training in the use of the vacuum device. The utilization of certified representatives from the supplier of the product provides a cost-efficient method of providing patient education without requiring the use of clinic staff/personnel, while enhancing patient compliance with therapy and should be given priority of consideration.

Table of Evidence

Intervention	References	Strength of Recommendation	Level of Evidence
First line therapy	1	I	C
Patient education	2	I	C

References

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2. Gould J E et al. External Vacuum Devices: A Clinical Comparison with Pharmacologic Erections. World J Urol. 1992;10:68-70.

3. Lewis, R & Withirington, R External Vacuum Therapy for Erectile Dysfunction: Use & Results. World J Urol.1997;15:78-82.

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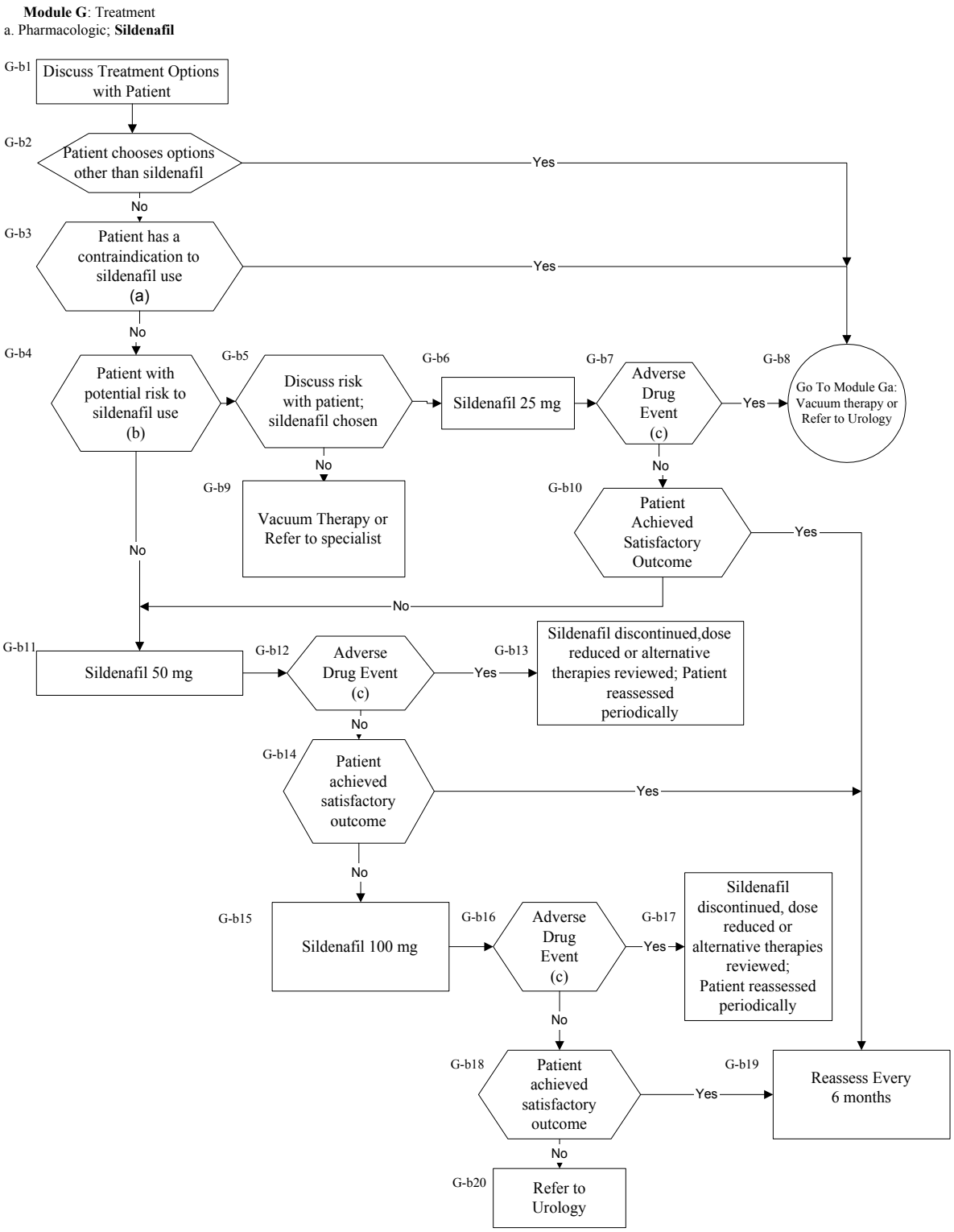

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Module G-b: Pharmacologic/**Sildenafil**

Objectives:

1. to describe the indications, efficacy and satisfaction, and treatment protocol including dose escalation
2. to characterize the absolute contraindications and the relative contraindications and other clinical conditions including concurrent medication administrations where sildenafil must be used with caution
3. to review other adverse effects of sildenafil

Annotation (a): Patient has a contraindication to sildenafil use.

Objective: To describe the indications, efficacy and satisfaction, and treatment protocol including dose titration.

Summary: Sildenafil is one of two initial therapies for ED available to primary care physicians. It is appropriate where there are no absolute contraindications and should be used with caution in some patients with relative contraindications (see Obj. (b) below). It may be considered first line therapy (along with use of the vacuum pump) after secondary etiologies of ED have been considered and eliminated when this is clinically reasonable. In patients at higher risk of adverse events the starting dose of sildenafil should be low, (25mg) and the evaluation interval earlier and more frequent than those patients at low risk. In patients at higher risk for adverse events (see Table 1) without an absolute contraindication for sildenafil and who desire therapy then sildenafil should be started at the lowest dose (25mg). The first dose may be given in the clinic and the vital signs monitored in the clinic. Initial prescription fills should give only limited supplies of sildenafil. These individuals should be reevaluated early and frequently and only slowly titrated up to the maximum 100mg dose (or 50mg dose in those using medications which raise serum concentrations of sildenafil see above). In patients at low risk for adverse events, the starting dose can be 50mg. However, the initial prescription should still be limited and the patient reevaluated for efficacy and adverse events. Based on information from other healthcare plans, the manufacturer of sildenafil and from sexual behavior studies, the number of tablets (of the effective dose) commonly prescribed ranges from 3 to 6 tablets per patient, per month. The manufacturer has provided prescription dispensing data, which shows the number of tablets prescribed per patient per month, is currently at four. VA practitioners may want to use the range as a reference point when prescribing sildenafil.

Annotation (b): Patient with potential risk to sildenafil use.

Objective: To characterize the absolute contraindications and the relative contraindications and other clinical conditions including concurrent medication administrations where sildenafil must be used with caution.

Summary: Sildenafil is absolutely contraindicated in patients using prescribed or recreational organic nitrates (see Table 2) and in patients with known hypersensitivity to sildenafil. In addition, sildenafil is relatively contraindicated and should be used with caution in a number of additional circumstances including clinical conditions associated with low blood pressure, administration of medications and chronic renal and hepatic diseases which may increase the serum concentrations or prolong the presence in serum of sildenafil. It does

not appear that sildenafil directly affects the heart. However, the use of sildenafil in patients with cardiac disease who are not currently taking nitrates is controversial and warrants substantial caution.

Discussion: The physiologic mechanism of erection of the penis involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. NO then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum but enhances the effect of NO by inhibiting phosphodiesterase type 5 (PDE 5), which is responsible for degradation of cGMP in the corpus cavernosum. When sexual stimulation causes local release of NO, inhibition of PDE 5 by sildenafil causes increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus carvernosum. Due to the distribution of orally administered sildenafil, smooth muscle relaxation is not limited to the penile vasculature but occurs systemically.

While use of sildenafil alone in normal individuals seldom reduces blood pressure, the combination of sildenafil and organic nitrates (as well as sildenafil in certain clinical conditions associated with hypotension) may cause life-threatening hypotension (see Table 3). This potential additive/synergistic effect means that the use of sildenafil in patients using nitrates and the use of nitrates to treat acute cardiac ischemic events (see Table 2) or malignant hypertension (nitroprusside) in patients who have recently taken sildenafil are contraindicated.

There are no controlled clinical data on the safety of sildenafil in patients with a number of clinical conditions. Table 1 is a list of these conditions where there may be clinical risk. The conditions can be divided into several categories (see Table 1).

1. **Cardiac disease.** FDA post-marketing surveillance documents a number of deaths associated with the use of sildenafil. Most of these deaths were due to cardiovascular etiologies. Most of these patients had readily apparent risk factors for cardiac disease including hypertension, hypercholesterolemia, etc. Therefore, in addition to the absolute contraindication in cardiac patients using nitrates, there are several categories of patients with cardiovascular disease where sildenafil should be used with caution. In addition there is a potential for cardiac risk of sexual activity in patients with preexisting cardiovascular disease (Table 1). Thus resumption of sexual activity with the use of sildenafil may also pose a similar risk. The post marketing surveillance of sildenafil is consistent with this. There is no evidence for a protocol to risk stratify these patients although it has been suggested that various exercise tests could aid in this determination.

2. **Complex multidrug antihypertensive therapy**. The initial studies did not include patients on multiple antihypertensive agents. Theoretically these individuals may be at higher risk of cardiac disease due to the hypertension and at greater risk of hypotension due to the added effect of sildenafil.

3. **Retinal disorders particularly Retinitis pigmentosa and macular degeneration**. Sildenafil may also alter PDE6 in the retina. This may produce a blue discoloration to vision. This effect appears to be transient. However, sildenafil is relatively contraindicated in patients with genetic retinal disorders including retinitis pigmentosa. The long-term retinal effects of sildenafil are unknown; routine follow-up eye examinations should be maintained, and providers should be alert to any unexpected or persistent visual symptoms.

Sildenafil should be used cautiously in individuals with other retinal disorders including macular degeneration and proliferative diabetic retinopathy. (See Appendix 3)

4. **Diseases and medications which alter metabolism of Sildenafil.**
   (See Table 4)

Annotation (c): Adverse Drug Event

Objective: To review other adverse effects of sildenafil.

Summary: The major adverse effects of sildenafil are related to vasodilation. The most significant of those effects is hypotension discussed above but also includes headache, flushing and nasal congestion. (See Table 4)

Table 1: High risk patients/clinical conditions for adverse effects with Sildenafil

ALTERED END ORGAN FUNCTION
- age 65
- hepatic impairment
- renal impairment

DRUGS WHICH RAISE PLASMA LEVELS/DELAY CLEARANCE OF SILDENAFIL (See Table 3)

CARDIAC
- complex multidrug antihypertensive regimens
- ischemic coronary artery disease not on nitrates
- uncompensated CHF
- hypotension (BP <90/50) of any etiology
- MI, stroke, or life-threatening arrhythmia within 6 months
- poorly controlled hypertension (170/110)
- unstable angina

RETINAL DISORDERS (See Appendix 3)
- retinitis pigmentosa
- macular degeneration

SPINAL CORD INJURY ABOVE T5-6 AT RISK FOR AUTONOMIC DYSREFLEXIA
PENILE PROBLEMS
- anatomic deformity (eg. angulation, Peronie's)
- history of priapism or high risk of priapism (eg. sickle cell disease)

MISCELLANEOUS
- bleeding disorders
- active peptic ulcer disease

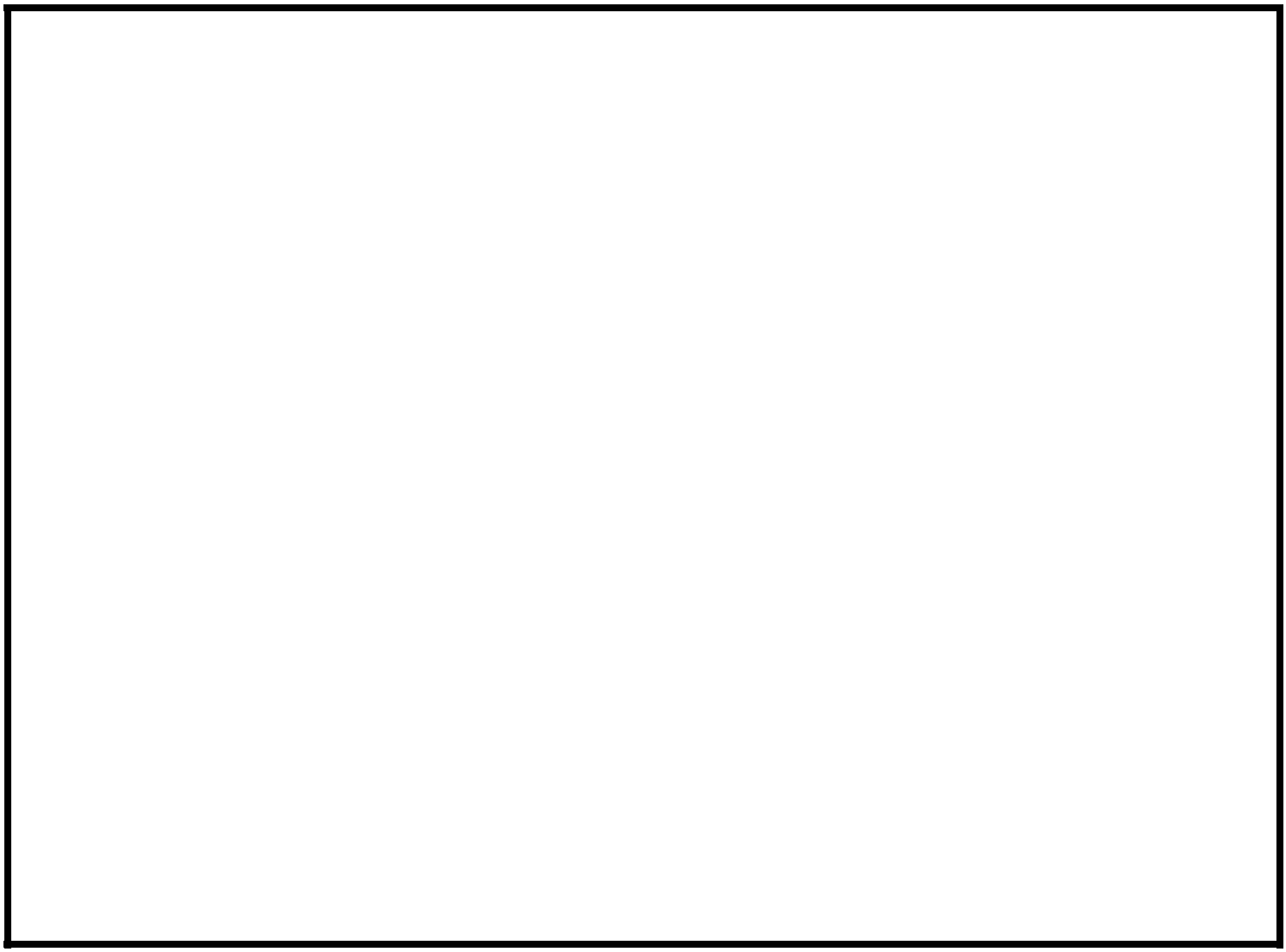

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Table 2: Organic Nitrates

Nitroglycerin	**Isosorbide Mononitrate**	**Isosorbide Dinitrate**	**Nitroprusside Sodium I.V.**	**Illicit Substances Containing Organic Nitrates**
Deponit Minitran Nitrek Nitro-Bid Nitrocot	Imdur ISMO Isotrate ER Monoket	Dilatrate-SR ISDN Iso-Bid Isordil Sorbitrate	Nitropress	Amyl nitrite (or nitrate), butyl nitrate; in abuse situations, may be known by various names, including "Liquid Gold," "poppers," "bang,"

Nitro Disc Nitro-Dur Nitrogard Nitroglyn Nitrol Ointment Nitrolingual Spray Nitro-Par Nitroquick Nitrospan Nitrostat Nitro-Time Transderm- Nitro Tridil I.V				"snappers," "flash"

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Note: While some of the brand names suggest that the product contain a nitrate other brand names do not give similar clues. Thus, it is imperative that the physician obtains a complete drug history in any patient being considered for sildenafil therapy.

Table 3: Treatment of the Hypotensive Patient with Inadvertent Sildenafil-Nitrate Combination

In patients who inadvertantly-received nitrates while taking sildenafil and who manifest a severe hypotensive response, *nitrate and nitroprusside (NO donor) therapy should be immediately stopped.* **Depending on clinical circumstances, any of the following therapies should be considered alone or in combination:**

- Place the patient in Trendelenburg position.

- Provide aggressive fluid resuscitation.
- Provide judicious use of an intravenous alpha-adrenergic agonist such as phenylephrine.
- Provide an alpha- and beta-adrenergic agonist (norepinephrine) for blood pressure support, with the realization that this could exacerbate or lead to an acute ischemic syndrome.
- Provide intra-aortic balloon counterpulsation

The ACC/AHA Expert Consensus Document. Use of Sildenafil (Viagra) in Patients With Cardiovascular Disease. Circulation 1999; 99:168-177.

Table 4: Factors which may **INCREASE** plasma concentrations of Sildenafil

	MEDICATIONS				
ALTERED END ORGAN FUNCTIONS	*ANTIDEPRESSANTS*	*ANTIFUNGALS*	*HIV PROTEASE INHIBITORS*	*MACROLIDES*	*OTHER*
• **Age 65 YO** • **Hepatic Impairment** Cirrhosis; 80% • **Renal Impairment** CrCl = 30 cc/min; 100%	• fluvoxamine (Luvox) • nefazodone (Serzone) • norfluoxetine (Prozac metabolite)	• fluconazole (Diflucan) • itraconazole (Sporanox) • ketoconazole (Nizoral)	• indinavir (Crixivan) • nelfinavir (Viracept) • ritonavir (Norvir) • saquinavir (Fortovase)	[NOT azithromycin] • clarithro-mycin (Biaxin) • erythro-mycin • troleando-mycin (Tao)	• amiodarone (Cordarone) • cimetidine (Tagamet) • ciprofloxacin (Cipro) • grapefruit juice

Physician Package Insert February 1999
Flockhart D. "Cytochrome P450 Drug Interaction Table" 04/16/99
www.dml.georgetown.edu/depts/pharmacology/davetab.html

Appendix 1: The International Index of Erectile Function (IIEF) in the Assessment of Erectile Dysfunction

Objective: To describe the IIEF and its role in the assessment and diagnosis of erectile dysfunction.

Summary: The IIEF is a 15 item, self-administered scale useful as one evaluation strategy in a comprehensive assessment of erectile dysfunction. The scale has been normed cross-culturally, is psychometrically sound with high reliability and validity, and demonstrates sensitivity and specificity for detecting changes in erectile functioning in patients with ED (1, 4, 5).

Discussion: As a brief and reliable measure of male sexual functioning, the 15 item IIEF was developed into its present form from the shorter Index of Erectile Dysfunction (4,5). It is a positive response to the recommendation of the NIH Consensus Conference for the development of a better and more reliable method of assessing the symptoms of ED (2). It is linguistically validated in ten languages and demonstrates sound psychometric properties (5).

A high degree of internal consistency has been evidenced for each of five domains (sexual desire, erectile function, orgasmic function, intercourse satisfaction, and overall satisfaction) and for the total scale (Cromabach's alpha values of 0.73 and higher and 0.91 and higher respectively). Test-retest reliability correlation coefficients for the five domains were highly significant (ranging from r=0.64 to 0.84 for individual domains and r-0.82 for total scale scores). Significant changes (P values = 0.0001) were demonstrated between baseline and post-treatment scores across all five domains in the treatment responder cohort, but not in the treatment nonresponder cohort. Hence, the IIEF demonstrates adequate sensitivity and specificity for detecting changes in erectile functioning in patients with ED (1, 4, 5).

Advantages of this scale include being self-administered and incorporating the major aspects of the NIH definition of ED within individual items (2, 4). It is brief and easy to comprehend by most patients, which provide practical value for clinical assessment in a primary care setting. Limitations are that it focuses upon current (last four weeks) functioning only and does not aid in developing a longer history of erectile functioning. Additionally, it has very limited value for evaluation of the partner relationship, which may be a contributing factor to the complaint of ED. Therefore, any written survey (such as the IIEF) should always be used as an adjunct to, rather than substitute for, a detailed sexual history (2, 4).

The IIEF has a range of scores from 5 to 75. Scores of 60 or more reflect normal erectile function. Scores of 30 or below indicate moderate to severe erectile dysfunction.

Table of Evidence

Intervention	Reference	Strength of Recommendation	Level of Evidence
Inclusion of International Index of Erectile Dysfunction (IIEF) or equivalent as assessment measure during initial of ED and as measure treatment progress	3 4,5 1	I I I	C B A

References

1. Goldstein I, et al. Oral sildenafil in the treatment of erectile dysfunction." The New England Journal of Medicine. 1998; 338 (20): 1397-1404.

2. NIH Consensus Development Panel on Impotence. NIH Consensus Conference on Impotence. JAMA. 1993; 270(1): 83-90.

3. Process of Care Panel, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School.The process of care model for the evaluation and treatment of erectile dysfunction. UMDNJ-Center for Continuing Education. 1998.

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5. Rosen R, et al. The international index of erectile function (IIEF): A multidimensional scale for assessment of erectile dysfunction. Urology. 1996;49(6): 822-830.

Attachments IIEF

INVESTIGATOR _____ DATE OF VISIT (month/day/year) ___/___/___

PLEASE USE A CROSS MARK ☒ WHERE APPLICABLE AND BE SURE TO INITIAL AND DATE ALL CORRECTIONS

☐ NOT DONE

SUBJECT QUESTIONNAIRE - Section 1

INSTRUCTIONS: These questions ask about the effects your erection problems have had on your sex life, over the past 4 weeks.
Please answer the following questions as honestly and clearly as possible. In answering these questions the following definitions apply:
Sexual activity includes intercourse, caressing, foreplay and masturbation
Sexual intercourse is defined as vaginal penetration of the partner (you entered your partner)
Sexual stimulation includes situations like foreplay with a partner, looking at erotic pictures, etc.
Ejaculate is defined as the ejection of semen from the penis (or the feeling of this)

Check ONLY one box per question:

1. Over the past 4 weeks, how often were you able to get an erection during sexual activity?
   - ☐ No sexual activity
   - ☐ Almost always or always
   - ☐ Most times (much more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (much less than half the time)
   - ☐ Almost never or never

2. Over the past 4 weeks, when you had erections with sexual stimulation, how often were your erections hard enough for penetration?
   - ☐ No sexual stimulation
   - ☐ Almost always or always
   - ☐ Most times (much more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (much less than half the time)
   - ☐ Almost never or never

The next three questions will ask about erections you may have had during sexual intercourse.

3. Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?
   - ☐ Did not attempt intercourse
   - ☐ Almost always or always
   - ☐ Most times (much more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (much less than half the time)
   - ☐ Almost never or never

4. Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
   - ☐ Did not attempt intercourse
   - ☐ Almost always or always
   - ☐ Most times (much more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (much less than half the time)
   - ☐ Almost never or never

Continued on next page

INVESTIGATOR _____ DATE OF VISIT (month/day/year) ____/____/____

NOTE: PLEASE USE A CROSS MARK ☒ WHERE APPLICABLE AND BE SURE TO INITIAL AND DATE ALL CORRECTIONS [redacted]

SUBJECT QUESTIONNAIRE *(continued)*

Check ONLY one box per question:

5. Over the past 4 weeks, during sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
   - ☐ Did not attempt intercourse
   - ☐ Extremely difficult
   - ☐ Very difficult
   - ☐ Difficult
   - ☐ Slightly difficult
   - ☐ Not difficult

6. Over the past 4 weeks, how many times have you attempted sexual intercourse?
   - ☐ No attempts
   - ☐ 1 – 2 attempts
   - ☐ 3 – 4 attempts
   - ☐ 5 – 6 attempts
   - ☐ 7 – 10 attempts
   - ☐ 11 or more attempts

7. Over the past 4 weeks, when you attempted sexual intercourse how often was it satisfactory for you?
   - ☐ Did not attempt intercourse
   - ☐ Almost always or always
   - ☐ Most times (much more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (much less than half the time)
   - ☐ Almost never or never

8. Over the past 4 weeks, how much have you enjoyed sexual intercourse?
   - ☐ No intercourse
   - ☐ Very highly enjoyable
   - ☐ Highly enjoyable
   - ☐ Fairly enjoyable
   - ☐ Not very enjoyable
   - ☐ Not enjoyable

9. Over the past 4 weeks, when you had sexual stimulation or intercourse how often did you ejaculate?
   - ☐ No sexual stimulation or intercourse
   - ☐ Almost always or always
   - ☐ Most times (much more than half the time)
   - ☐ Sometimes (about half the time)
   - ☐ A few times (much less than half the time)
   - ☐ Almost never or never

Sexual activity includes intercourse, caressing, foreplay and masturbation
Sexual intercourse is defined as vaginal penetration of the partner (you entered your partner)
Sexual stimulation includes situations like foreplay with a partner, looking at erotic pictures, etc.
Ejaculate is defined as the ejection of semen from the penis (or the feeling of this)

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INVESTIGATOR _____ DATE OF VISIT (month/day/year) ____/____/____

PLEASE USE A CROSS MARK ☒ WHERE APPLICABLE AND BE SURE TO INITIAL AND DATE ALL CORRECTIONS [redacted]

SUBJECT QUESTIONNAIRE *(continued)*

Check ONLY one box per question:

10. Over the past 4 weeks, when you had sexual stimulation or intercourse how often did you have the feeling of orgasm or climax (with or without ejaculation)?
    - ☐ No sexual stimulation or intercourse
    - ☐ Almost always or always
    - ☐ Most times (much more than half the time)
    - ☐ Sometimes (about half the time)
    - ☐ A few times (much less than half the time)
    - ☐ Almost never or never

The next two questions ask about sexual desire.
Let's define Sexual Desire as a feeling that may include wanting to have a sexual experience *(for example masturbation or intercourse)*, thinking about having sex, or feeling frustrated due to lack of sex.

11. Over the past 4 weeks, how often have you felt sexual desire?
    - ☐ Almost always or always
    - ☐ Most times (much more than half the time)
    - ☐ Sometimes (about half the time)
    - ☐ A few times (much less than half the time)
    - ☐ Almost never or never

12. Over the past 4 weeks, how would you rate your level of sexual desire?
    - ☐ Very high
    - ☐ High
    - ☐ Moderate
    - ☐ Low
    - ☐ Very low or none at all

13. Over the past 4 weeks, how satisfied have you been with your overall sex life?
    - ☐ Very satisfied
    - ☐ Moderately satisfied
    - ☐ About equally satisfied and dissatisfied
    - ☐ Moderately dissatisfied
    - ☐ Very dissatisfied

14. Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?
    - ☐ Very satisfied
    - ☐ Moderately satisfied
    - ☐ About equally satisfied and dissatisfied
    - ☐ Moderately dissatisfied
    - ☐ Very dissatisfied

15. Over the past 4 weeks, how do you rate your confidence that you can get and keep your erection?
    - ☐ Very high
    - ☐ High
    - ☐ Moderate
    - ☐ Low
    - ☐ Very low

Sexual activity includes intercourse, caressing, foreplay and masturbation
Sexual intercourse is defined as vaginal penetration of the partner (you entered your partner)
Sexual stimulation includes situations like foreplay with a partner, looking at erotic pictures, etc.
Ejaculate is defined as the ejection of semen from the penis (or the feeling of this)

[redacted]

International Index of Erectile Function Questionnaire (US version)	
Question	Response Options
Q1: Over the past 4 weeks, How often were you able to get an erection during sexual activity? Q2: Over the past 4 weeks, When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	0 = No sexual activity 1 = Almost never/never 2 = few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
Q3: Over the past 4 weeks, When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner? Q4: During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	0 = Did not attempt Intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
Q5: Over the past 4 weeks, During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	0 = Did not attempt Intercourse 1 = Extremely difficult 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
Q6: Over the past 4 weeks, How many times have you attempted sexual intercourse?	0 = No attempts 1 = One to two attempts 2 = Three to four attempts 3 = Five to six attempts 4 = Seven to ten attempts 5 = Eleven + attempts
Q7: Over the past 4 weeks, When you attempted sexual intercourse, how often was it satisfactory for you?	0 = Did not attempt Intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
Q8: Over the past 4 weeks, how much have you enjoyed sexual intercourse?	0 = No intercourse 1 = Very highly enjoyable 2 = Highly enjoyable 3 = Fairly enjoyable 4 = Not very enjoyable

	5 = Not enjoyable
Q9: Over the past 4 weeks, When you had sexual stimulation or intercourse, how often did you ejaculate? Q10: Over the past 4 weeks, When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax? With or without ejaculation?	0 = No sexual stimulation/intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
Q11: Over the past 4 weeks, How often have felt sexual desire	1 = Almost never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
Q12: Over the past 4 weeks, How would you rate your level of sexual desire?	1 = Very low/none at all 2 = Low 3 = Moderate 4 = High 5 = Very high
Q13: Over the past 4 weeks, How satisfied have you been with your overall sex life? Q14: Over the past 4 weeks, How satisfied have you been with your sexual relationship with your partner?	1 = Very dissatisfied 2 = Moderately dissatisfied 3 = About equally satisfied and dissatisfied 4 = Moderately satisfied 5 = Very satisfied
Q15: Over the past 4 weeks, How do you rate your confidence that you could get and keep an erection?	1 = Very low 2 = Low 3 = Moderate 4 = High 5 = Very High

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SCORING ALGORITHM FOR IIEF

All items are scored in 5 domains as follows:

DOMAIN	ITEMS	SCORE RANGE	MAXIMUM SCORE
Erectile Function	1,2,3,4,5,15	0-5	30
Orgasmic Function	9,10	0-5	10
Sexual Desire	11,12	1-5	10
Intercourse Satisfaction	6,7,8	0-5	15
Overall Satisfaction	13,14	1-5	10

CLINICAL INTERPRETATION:

I. **Erectile function** total scores can be interpreted as follows:

Score	Interpretation
0-6	Severe dysfunction
7-12	Moderate dysfunction
13-18	Mild-to-moderate dysfunction
19-24	Mild dysfunction
25-30	No dysfunction

II. **Orgasmic function** total scores can be interpreted as follows:

Score	Interpretation
0-2	Severe dysfunction
3-4	Moderate dysfunction
5-6	Mild-to-moderate dysfunction
7-8	Mild dysfunction
9-10	No dysfunction

III. **Sexual Desire** total scores can be interpreted as follows:

Score	Interpretation
0-2	Severe dysfunction
3-4	Moderate dysfunction
5-6	Mild-to moderate dysfunction
7-8	Mild dysfunction
9-10	No dysfunction

IV. **Intercourse Satisfaction** total scores can be interpreted as follows:

Score	Interpretation
0-3	Severe dysfunction
4-6	Moderate dysfunction
7-9	Mild-to-moderate dysfunction
10-12	Mild dysfunction
13-15	No dysfunction

V. **Overall Satisfaction** total scores can be interpreted as follows:

Score	Interpretation
0-2	Severe dysfunction
3-4	Moderate dysfunction
5-6	Mild-to-moderate dysfunction
7-8	Mild dysfunction
9-10	No dysfunction

Appendix 2: Basic Erectile Dysfunction Patient Education for use by Providers with Patients and Partners.

DEFINITION

Erectile dysfunction (ED) is defined as the consistent inability to get or keep an erection sufficient for intercourse. ED is the new name for sexual impotence**.**

INCIDENCE AND EFFECTS

Erectile dysfunction is only one of several types of sexual dysfunction. It has a great impact on other medical conditions, on psychological outlook and psychosocial behavior. It effects a man's health, relationships, and sense of well being. It is closely associated with depression. If you are diabetic and your diabetes causes erectile dysfunction, and your erectile dysfunction causes depression, depression can then cause your diabetes to get worse because you do not feel like exercising or eating properly. A vicious self-propelling cycle can occur.

The National Institute of Health has estimated that 30 million men in the United States suffer from erectile dysfunction. Before Viagra was widely advertised, only about three million men were being treated for this problem. That meant that only one out of every ten men, with erectile dysfunction, was receiving treatment. **The prevalence of ED increases with age.** If you look at the statistics from the Massachusetts Male Aging Study (a general questionnaire that was sent out to men in Massachusetts and asked all types of health questions) they found that **48% of all men over the age of 50 have some degree of erectile dysfunction. Over the age of 70, 67% of all men have some degree of ED.**

ED has a huge social impact. It can cause problems with partners and end significant relationships. For single men that are not in a relationship, it is very difficult for them to form relationships with potential sex partners and even with friends because they think that they are the only one with this problem. **There are three things patients and their partners need to understand:**

1. ED is most often a medically caused condition (like diabetes and hypertension)
2. ED patients are not alone
3. Effective treatments for ED exist

CAUSES

In physical erectile dysfunction or impotence:

- 40% is caused by vascular dysfunction
- 30% by diabetes
- 5% by neurological diseases (spinal cord injury, ms, Parkinson's disease, neuropathy caused by other diseases, etc.)
- 8% by surgery
- 15% by medications
- 2% for hormone deficiency

Some of these medical conditions are associated with so called **"lifestyle factors"**, which contribute to the development of ED. These factors include the *use of tobacco, alcohol and several illicit drugs*. Finally, ED can

also be caused by **psychological factors** such as *depression, anxiety, guilt, sexual abuse and conflict with a relationship*. Very often, a man may have two or more factors contributing to his ED.

MYTHS AND MISCONCEPTIONS

One myth about ED is that it is solely a psychological problem. This myth came out of Masters and Johnson's definitive book on sexual functioning published in 1970. In the book, the authors state that between 80-90% of all erectile dysfunction was psychological and emotional in nature. **Now medicine knows this is not true.** In the 1980's, medicine was able to look at all arteries, veins and nerves that supplied the penis. It was found that 85% of men with erectile dysfunction had physical dysfunction. They were able to note arterial damage or vein closure damage or nerve damage. Only about 15% were "purely psychological", and even those case leave questions as to whether there is a physical component.

Rarely is an erection problem purely physical or psychological. Typically, ED involves some arterial problems, some vein closure problems, some nerve damage and a psychological component. Once a man has his first erection failure, the next time he is in a sexual situation a voice goes off in the back of his head saying, "Ugh, oh! I am in trouble now". Even for patients with a clear physical cause to their ED, like radical prostate surgery, there is still anxiety and stress which makes matters worse. There is always a psychological component to ED, but psychological factors are the primary cause in only a minority of cases.

A second myth is that all cases of ED can be successfully treated with testosterone. Too low a level of testosterone is cause of ED in only 2% of all cases. Therefore, only 2 out of 100 patients with ED may have their ED respond to testosterone replacement therapy. This relates to sexual desire (or libido). If a man has ED and his sexual desire is normal, testosterone is probably not going to be an effective therapy for his ED.

TYPES OF SEXUAL DYSFUNCTION

There are five components to normal male sexual function: libido (sexual desire), arousal (when erection occurs), orgasm, ejaculation and resolution. They are actually five completely separate functions. Normally they work seamlessly together, but they are five independent processes. You might have normal desire but are unable to get an erection. With nerve damage, as in spinal cord injury, it is possible to get erections without desire; these are reflex erections. It is also possible to have an orgasm without an erection and an orgasm without ejaculation.

Sexual libido is the desire for sex or the sex drive. It is controlled by the brain, mediated by testosterone, and when stimulated results in the initiation of the arousal response

Erectile function is the physical component. It is a natural result of the sexual stimulation and includes libido. It is the filling of the chambers; the conduction of the nerve impulse to the erection chambers, the opening of the arteries, and the closing of the veins. The integration of these physical components results in a man having an erection. That is not meant to minimize the psychological factors. There are partnership, relationships and personal problems that can cause and are caused by erectile dysfunction. **Psychological, sexual or relationship counseling can be very beneficial in the treatment of sexual dysfunction.**

Sexual climax or orgasm is a neurologic function. A man can have an orgasm without having an erection and he can have an erection without having an orgasm. If he is unable to have orgasm, it might be a sign of nerve

damage or neuropathy. However, if he does not have an erection and unable to orgasm, it may simply mean that there is not enough stimulation to the nerves. Sexual climax or orgasm problems may need alternative or additional therapies than those for erectile dysfunction.

Ejaculation is the ejection of the sperm and seminal fluids from the urethra in conjunction with orgasm. Most people think that ejaculation and climax (orgasm) are one in the same thing. They are not. When a man has an orgasm, he ejaculates because there is a contraction in the prostate and a release of seminal fluid. The majority of the fluid for the ejaculate is produced in the prostate gland. As men age, they develop prostate enlargement or benign prostate hyperplasia (BPH). They may not produce as much ejaculate because of this enlargement or the enlargement may block the passage of the ejaculate. When there is prostate enlargement that actually blocks the urethra, the ejaculate may go backwards into the bladder and is called retrograde ejaculation. If the urine is cloudy after sex, there may have been retrograde ejaculation. Surgery on the prostate gland may affect or completely stop the production of ejaculate.

Resolution is the part of sexual functioning when the man returns to an unaroused state (loses his erection), usually after ejaculation and orgasm. If a man's erection continues past several hours, he has a painful condition called *priaprism*, and needs to seek immediate medical attention.

PATHOPHYSIOLOGY OF ERECTILE DYSFUNCTION

An erection is a circulatory event. It involves blood flowing in and blood being trapped in the erection chamber. Once the brain is stimulated, the nerves conduct down the spinal cord to the pelvic nerves. The pelvic nerves then release a chemical or neurotransmitter. Prostaglandin (PGE1) is one of the neurotransmitters that are released, and a man made form of this chemical, Alprostadil, is one of the drugs uses in the treatment of erectile dysfunction. PGE1 causes the arteries to open up and the blood to flow in and causes the erection chamber to relax and the veins to close off resulting in blood being trapped.

It was thought that the blood flowed in, and the pressure of the blood flowing in like a tire expanded the erection chamber until it pinched off the veins, and then blood did not flow out. It has been found that that is not true. There is actually a relaxation of the erection chamber. In a non-erect chamber the veins are wide open, anything that comes in drains right back out.

In an erect chamber, the veins are actually closed off and squeezed shut. That is how *anti-hypertensive medications* cause ED. Anti-hypertensives chemically work to decrease your blood pressure, but they also keep your erection chambers constricted. What happens is blood flows in, and it may expand the chambers some, but the man does not get the relaxation of the chamber and the blood flow out.

If you think of it as a bathtub effect, the nerves are what turn on the faucet and put a plug in the drain. They open up the arteries; they open up the erection chamber to close off those veins. The arteries are the inflow (or faucet) and the veins are the plugs at the bottom of the drain. If the erection chamber has not relaxed, and the veins are not closed off, then blood is going to leak fluid right back out of those veins. If you have ever tried to fill a bathtub with the plug out, sometimes you can fill it up, but once you fill a certain level it drops off. If you turn off the faucet (or arterial inflow) or decrease it at all, you get a sudden loss of filling or erection. That is what happens with a vein closure (or veno-occlusion) problem. **A brief discussion follows on the four types of dysfunction which cause ED: arterial, vein, nerve and psychogenic.**

Arterial Dysfunction

Cigarette smoking is the number one contribute to erectile dysfunction. It works two ways. Number one, cigarette smoking damages penile arteries in the same way it damages coronary arteries. The second way that it works is that it causes spasm in small peripheral blood vessels. The blood to the penis is blood to the periphery in small vessels. Cigarette smoking is a huge component of erectile dysfunction. Hypertension causes damage to arteries and can cause erectile dysfunction if not controlled. Elevated cholesterol levels over a period of time can cause damage to arteries. Anything that can cause heart problems and causes damage to heart arteries causes erectile dysfunction.

Vein/veno-occlusion dysfunction

Vein/veno-occlusion problems are caused by pelvic or perineal trauma: falling on the crossbars of a bike when young; getting kicked in the groin when playing football; pelvic, perineal or abdominal surgeries; radical prostatectomies, some bladder surgeries, large abdominal surgeries including those with ostomies; diabetes; and medications can cause vein leakage problems. The medicines that cause veno-occlusion problems are most often heart medicines and all anti-hypertensives.

Nerve Dysfunction

Nerve problems are caused by spinal cord injuries, diabetes, excessive alcohol consumption, pelvic/perineal traumas, spinal cord injuries, Parkinson's disease, multiple sclerosis, any neurological diseases, pelvic perineal surgeries, radical prostatectomies, and TURP (transurethral resection of the prostate).

Psychogenic Dysfunction

The psychogenic effect is the fourth component and sometimes is referred to as the stress component. When a *body* is stressed by anything (upset by a relationship, a fight with the boss, had to work late, fatigue, a back injury with chronic pain, cancer, heart problems, etc.) it *deals with that stress by releasing catecholamines*. Catecholamines are a big group name for neuro-transmitters that basically prepare the body for the flight-fight syndrome. Anything that can cause a release of a *catecholamine can block an erection,* because the neuro-transmitters that cause erections have the opposite effect from the catecholamines.

If a patient is at a minimal level of erectile functioning, and a stressor is added, he can be pushed into the nonfunctioning category. That does not mean that the problem is primarily psychological or stress related, it means that stress is one component and that may have been the final component to contribute to ED. That is why people will function normally when they go away on vacation, because their normal life stresses are not there and their body is not producing catecholamines. It does not mean that the problem is purely psychogenic. It means you may have physical components, and the psychogenic or stress components make it better or make it worse depending on how severe they are.

TREATMENT OPTIONS

Sexual Counseling

Almost everybody that has ED has some psychogenic components. The question is how severe they are. Most of the time ED is caused by a medical problem and when you start treatment, you can actually overcome the psychogenic component. If ED happened around the loss of a relationship or caused the loss of a relationship, counseling may be necessary in addition to medical treatment to help overcome the psychogenic aspect of the erectile dysfunction. *If the ED is primarily caused by psychological factors (such as anxiety or conflict), sexual counseling is considered a "first line" therapy and may be the treatment of choice.* Concurrent counseling and use of other treatment options often improves outcomes and patient satisfaction.

Vacuum Erection Devices

Vacuum erection devices (or VED's) are also considered first line therapy, because they do not involve adding medications into the body. VED's do not cause any long-term side effects. It is basically a vacuum cylinder (a pump). The cylinder is placed over the penis and all the air is pumped out. Mechanically, the vacuum is created and draws blood in to the penis. A ring is then placed at the base of the penis to keep the blood there. It is a hand-held device and it is fairly simple to use. **It is non-surgical and it is effective 90-95% of the time.**

This means that if somebody who knows how to use the vacuum device, puts a vacuum device on his penis, pumps it up, puts the rings on, 90-95% of the time they are going to get a usable erection. That does not mean that the VED is going to be a satisfactory treatment for every patient, or that the patient is going to be able to use it effectively. It does mean that the VED can introduce a satisfactory erection. VED's do require practice and some manual dexterity in getting used to using it.

If used aggressively VED's can cause some mild bruising initially. Some patients do not like it; especially single men who do not have a regular sex partner, and/or are out there dating. It is real difficult to sneak into the bathroom, spend ten minutes and come back with an erection and a band at the base of your penis, and explain to somebody (you do not necessarily know that well) how you got the erection. This will most probably end up in a discussion and the mood is lost. So it is very difficult when dating to use a vacuum erection device.

It is also very difficult if the partner is not a willing participant in using a VED. Partners should be encouraged to participate fully. It is extremely important to get information out to partners about what is going on. If partners are not involved with the use the vacuum device, one or both people may lose interest and it can be a very frustrating situation for all involved. If the device is used as a couple, most people like it. If that is not the situation, there may be a better therapy choice.

Local Pharmacotherapy

Local pharmacotherapy means a medication does not go into the whole body, so it does not effect other organs. A common local medication used is Prostaglandin. There are two routes of administration for that drug: MUSE (a urethra suppository in an applicator) and penile injections. There are lots of different names for Prostaglandin: PGE1, Alprostadil, Caverject, MUSE, etc. They are the same drugs.

MUSE

MUSE is a medication with a little applicator that goes into the urethra. It is a very small, smooth plastic device with a suppository inside it. Once it is in place, a button is pushed down which pushes the suppository out into the urethra where it is absorbed. It comes pre-packaged, it is easy to use, and effective. It has a 30-60% efficacy rate. It works in about 5-10 minutes, usually lasts for 30-60 minutes- depending on the dosage and individual response.

Some people will lose their erection when they ejaculate, some people will not. If your partner is pregnant, use condoms with the MUSE. It has not been tested with couples where the partner was pregnant. They have looked at the amount of drug that was in the ejaculate which was equivalent to what your body normally produces, but it may have an adverse effect on a pregnant woman.

One out of four people get an aching side effect to it. With some people it is mild, some people it is more intense. The etiology is unclear but for some reason Alprostadil stimulates a pain response in about 25% of the people that use it. It sometimes happens after use within 10 to 40 minutes. It is an aching that may be in the testicles, the backs of the legs, the buttocks. It is difficult to predict whose will have this type of response. It is also very difficult to predict when you are going to have the response and how intense it is going to be.

As far as urethra pain, there might be some *burning pain the first few times* they use it, because they are not used to getting medicines via urethra. If they are gentle with the applicator, it is usually not a problem. Disadvantages include MUSE requires administration of medication. Fatigue, alcohol consumption and stress can affect the response to the medicine. This has to do with the same things that affects normal erection function. With MUSE body position affects whether the drug works. So if patients use MUSE and lay flat on their back, sometimes they will lose the erection.

Penile Injection Therapy

A small needle is used for injection into the base of the penis because the shaft of the penis is not as sensitive. The injection is into the erection chamber. Because the doses are so small, the people that have pain, refer to it as mild aching that does not disturb them. Scar tissue formation can occur if the patient does not rotate needle sites. Scar tissue formation is more prevalent in injections when papavarine is used, not as much of a problem with Alprostadil.

Prolonged erection is the most common side effect with injection treatment. If the dose is too high the patient can end up with an erection that lasts four, five, six hours. After two hours, it hurts; after four hours the patient begins having permanent tissue damage because he does not have blood flowing into the penis to get rid of the waste products from cells. It is important to be very careful about test dosing and be very cautious. *Another side*

effect is bruising. It is also important to hold pressure on the injection site for the two to three minutes after injection. The medicine is adversely affected by fatigue, alcohol consumption, and stress; the same is true of MUSE.

Surgery/Penile implants (Prosthesis)

Penile implants are a last resort because they require removal of tissue in the penis to put the implant in. If the patient decides he does not like the implant, it is too late for other therapies to be effective. A man does not have anything that the vacuum device or medications can really work on because the tissue has been removed. **Surgery is not first line of therapy, it is the last choice if everything else does not work because of the irreversibility of it.**

There are two different types of penile implants. There are *semi-rigid rods* that basically bend out of the way. When they are straightened, they have some rigidity, and allow for penetration. There is, however, always going to be some fullness, even when they are bent out of the way. The *inflatable implant* is the other type of penile prosthesis. It consists of inflatable rods that are placed in each erection chamber, a reservoir of fluid that sits up in the perineal cavity, and the pump that sits in the scrotum. It is pumped up to cause an erection and released to deflate. The prosthesis stays erect as long as you leave it pumped. It is effective and it is always there. There is no worry about going on vacation and forgetting it, because it is inside the body, and it does have good patient/partner satisfaction for the most part.

Penile implants are not perfect. A surgical procedure is required with a very small risk of infection. Every device that is man-made has a potential to fail. These implants are very good devices with very few failures, but even pacemakers and cardiac valves fail sometimes. If they fail, another surgery is necessary. Penile implants typically last 15-20 years. For a patient in his 60's, he may be looking at two or three implants while he is still sexually active. Do not assume that there is a time or age limit on sexual functioning. Perspectives change. Patients can enjoy sexual pleasure all their lives, including sexual functioning in their 90's.

Hormone replacement therapy

Hormone replacement therapy should only be pursued if the libido is low and testosterone is low. If hormone replacement therapy is needed it should be done with testosterone and monitored closely. *Yohimbine* is an over-the-counter herb/drug that will increase your testosterone level. It, however, can cause liver toxicity and hypertension, in addition to all of the risks of hormone replacement therapy. *The greatest risk factor with testosterone replacement is that it can increase rate of growth of prostate cancer cells, sort of a "fertilizer" for prostate cancer.* So if prostate cancer is a concern (such as a family history of prostate cancer or a history of elevated PSAs), serious consideration is wise before beginning this therapy.

Natural Supplements

If a patient has had prostate cancer, many of the herbal supplements for ED have *Yohimbine* in them. *Yohimbine is going to increase the testosterone level. This should be avoided if there is a history of prostate*

CA. Patients need to be very careful with the plethora of "erection cures", that may include Ginseng and Vitamin E

Lifestyle adjustments

The following are important guidelines for men who wish to make healthy lifestyle choices that reduce their risk for ED as well as promote their optimal sexual functioning:

- stop smoking
- light regular exercise (i.e.-walking two or three times a week)
- low fat and low cholesterol diet
- increased dietary fruits and vegetables
- dietary supplements
- drink alcohol only in moderation
- do not use illicit drugs (those having adverse effects on erectile functioning are amphetamines, cocaine, heroin, marijuana, morphine, and steroids)

SUMMARY

With the aid of health care providers, each patient is going to have to find the optimal treatment for himself. No one can make this type of personal decision for him and his partner. The primary care practitioner can guide patients toward an effective treatment choice and help them keep an open mind. The treatment options patients initially desire might not work or be the best choice for them. Another treatment option or a combination of treatments may increase patient satisfaction and improve outcomes.

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Appendix 3: Ophthalmic Evaluation

Objective: To describe the ophthalmic evaluation of patients with erectile dysfunction treated with sildenafil.

Summary Annotation:
The etiology of erectile dysfunction (ED) is complex and multi-factorial. ED has a strong association with aging with a two- to three-fold increase in prevalence of moderate-to-severe ED between the ages of 40 and 70 years. Patients in this age group are also those likely to require ophthalmic care for ocular disorders of aging. Some of these include age-related macular degeneration (ARMD), diabetic retinopathy, hypertensive retinopathy, and glaucoma. One of the potential pharmacological treatments for ED is the medication sildenafil (Viagra; Pfizer Pharmaceuticals). The therapeutic action of sildenafil in the treatment of ED is as a selective inhibitor of phosphodiesterase 5 (PDE-5) in the vascular smooth muscle of the corpora cavernosa of the penis. Although no long-term ophthalmic side effects of sildenafil have yet to be reported, there is potential ophthalmic risk based on the critical role of phosphodiesterase 6 (PDE-6) in the photoreceptor transduction process. Patients with retinal diseases with etiologic disorders of photoreceptor function, e.g., ARMD and retinitis pigmentosa (RP), may be particularly susceptible. Of further potential concern is the vasodilatory action of sildenafil with potential consequences in vasculopathic diseases of the retina, e.g., diabetic retinopathy.

Discussion: ARMD and RP
Although sildenafil was designed as a selective inhibitor of PDE-5 it is known to have a 10-fold lower affinity for PDE-6, the isoform critical in the photoreceptor transduction process. The photoreceptor outer segments have a high concentration of cGMP in the dark, which maintains current flow through sodium channels. Upon light exposure, PDE-6 is activated to break down cGMP and close these channels. This hyperpolarization is the initial neural event in the visual process. Pharmacologic inhibition of PDE-6 may consequently reduce this light inactivation of cGMP and alter the transduction process. This is the likely explanation for the dose-dependant visual symptoms of bluish tinged and/or hazy vision and increased light sensitivity reported by some patients treated with sildenafil. To date no long term symptoms have been documented in clinical trials but little information on long-term objective data is available in the scientific peer-reviewed literature. In clinical studies reported at the meeting of the Association for Research in Vision and Ophthalmology (May 9-14, 1999, Fort Lauderdale, Florida) only transient, dose-dependent, and reversible alterations in electroretinographic responses (delayed implicit time), and color vision were reported. There may be some reasons for concern, however, as animals with hereditary abnormalities in the PDE-6 gene have demonstrable evidence of long-term photoreceptor degeneration. Furthermore, animals treated with very high doses show a loss of amplitude and a delayed electroretinographic response although no retinal degeneration was observed even after one year.

Patients with diseases of the photoreceptor layer, e.g., ARMD and RP, may be particularly susceptible. Those patients at highest risk are those with a particular type of autosomal recessive RP with defects in the PDE-6 gene or unsuspecting heterozygote carriers.

Discussion: Diabetic retinopathy

The direct vasodilatory action of sildenafil might be reflected in the eye with an increase in choroidal or retinal blood flow. This latter action may have potential consequences in vasculopathic diseases of the retina such as diabetic retinopathy. The known pathophysiology of diabetic retinopathy includes microaneurysm formation and neovascularization of the retina. Vasodilation in this setting may hypothetically lead to increased potential for intraretinal or intraocular hemorrhage, or have other, as yet, unforseen sequelae. Longer term follow up of susceptible patients may be necessary before these hypothetical consequences can be proven or disproven.

Protocol:

Given the unknown long-term consequences of sildenafil use the following evaluation protocol is suggested for all patients considered for sildenafil therapy for ED:

- Obtain an ophthalmic history (including family history) with particular emphasis on retinal disease.
- If no evidence of ophthalmic exam within the past two years refer for baseline ophthalmic exam including indirect ophthalmoscopy.
- If patient with diagnosis of RP or ARMD or known or suspected family history of RP, counsel on the reported short term side effects and unknown long-term side effects of sildenafil use and particular concern of potential adverse effects in RP and ARMD. In addition, careful adherence to treatment regimen must be emphasized with avoidance of higher doses recommended. Reporting of unusual visual side effects and close follow-up with ophthalmologist also needed.
- If patient with diagnosis of retinal vascular disease, e.g., diabetic retinopathy, counsel on the reported short term side effects and unknown long-term side effects of sildenafil use and particular concern in vascular retinopathic diseases, such as, potential for increase hemorrhagic sequelae. In addition, careful adherence to treatment regimen must be emphasized with avoidance of higher doses recommended. Reporting of unusual visual side effects and close follow-up with ophthalmologist also needed.

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