

Supplementary Material

Article Title: Psychotropic Medication-Induced Priapism: An Approach to Diagnosis and Treatment

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

1. **Supplementary Appendix A**
2. **Supplementary Appendix B**

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Supplementary Appendix A

Table 1. Comprehensive List of Medications Associated With Drug-Induced Priapism

Elevated risk medications are bolded, with the percentages of the individual cases of priapism in Schifano and colleagues' review of the US Food and Drug Administration Adverse Event Reporting System pharmacovigilance database arranged in relative order of incidence by class^{7,12,18}

Medication class	Medications
Antipsychotics	<u>Atypical</u> : Quetiapine (12.48%), risperidone (10.54%), olanzapine (8.60%), aripiprazole (6.49%), clozapine (2.51%), paliperidone, iloperidone, ziprasidone <u>Typical</u> : Chlorpromazine, fluphenazine, trifluoperazine, haloperidol, thioridazine, zuclopenthixol, pipamperone
Antidepressants	<u>SARIs</u> : Trazodone (15.98%) <u>SSRIs</u> : Sertraline (4.70%), citalopram, escitalopram, fluoxetine, paroxetine <u>SNRIs</u> : Venlafaxine, duloxetine, atomoxetine <u>NDRIs</u> : Bupropion
CNS stimulants	Methylphenidate (2.68%), dexamethylphenidate, lisdexamfetamine
Vasoactive erectile agents	Sildenafil (3.16%), tadalafil (6.00%), alprostadil (2.60%) (intracavernosal injection), papaverine (intracavernosal injection)
Alpha-adrenergic receptor antagonists	<u>Selective</u> : Tamsulosin, terazosin <u>Nonselective</u> : Doxazosin, prazosin
Anesthetics	Morphine (epidural), propofol
Hormonal therapy	Testosterone enanthate, gonadotropin releasing hormone, androstenedione, cabergoline/bromocriptine
Anxiolytics	Hydroxyzine
Antihypertensives	Hydralazine, guanethidine, propranolol
Anticoagulants	Unfractionated heparin, low molecular weight heparin, warfarin, acenocoumarin
Chemotherapy	Oxaliplatin
Dopamine agonist	Rotigotine
Herbal supplements	Tribulus terrestris, Rhino 7 Platinum 3000, All Nite Long, horny goat weed
Anticonvulsant	Topiramate, valproate, pregabalin, gabapentin, lamotrigine
Monoclonal antibody	Adalimumab
Antibiotics	Vancomycin
Melanocortin	Melanotan-II
Parenteral nutrition	20% fat emulsion
Recreational substances	Cocaine, cannabis, MDMA, alcohol

SARIs: serotonin receptor antagonists and reuptake inhibitors

SSRIs: selective serotonin reuptake inhibitors

SNRIs: serotonin and norepinephrine reuptake inhibitors

NDRIs: norepinephrine and dopamine reuptake inhibitors

MDMA: 3,4-methylenedioxymethamphetamine

Supplementary Appendix B

Table 2. Agents Used to Treat or Prevent Subsequent Episodes of Priapism

Medication/FDA Indication and Off-Label Uses	Mechanism of Action for Priapism	Typical Dose	Dosing Strategies for Priapism	Common Side Effects	Serious Reactions	Caution/Other Information
HORMONAL THERAPIES						
GnRH agonists						
Leuprolide acetate Central precocious puberty, endometriosis, advanced prostate cancer, uterine leiomyoma Off label: premenopausal ovarian preservation during chemotherapy and endocrine therapy, breast cancer in male patients, hormone therapy for transgender males, paraphilias (male)	Central androgen ablation; causes initial increase in FSH and LH; chronic use leads to suppression of pituitary gonadotropins with serum testosterone levels comparable to surgical castration	<u>Adult:</u> 3.75 mg every 4 weeks (endometriosis) 7.5 mg every 4 weeks (prostate cancer); available in long-acting injectable formulations (45 mg every 6 months) <u>Pediatric:</u> Weight-directed dosing: 7.5 to 15 mg every 4 weeks Fixed dosing: 7.5 mg every 4 weeks	Men: 7.5 mg every 4 weeks; 45 mg every 6 months	ECG changes, hypertension, ischemia, peripheral edema, diaphoresis, pruritis, abdominal pain, constipation, diarrhea, nausea, vomiting, psychiatric side effects, fever, fatigue	Decreased bone density, hypersensitivity reactions, cardiovascular events, pituitary apoplexy, psychiatric side effects, QT prolongation, seizures, tumor flare, gynecomastia (men), decreased libido (men)	Used for refractory cases due to poor tolerability; 50% efficacy with preventing future priapism episodes
Goserelin acetate Advanced breast cancer, endometrial thinning, endometriosis, advanced prostate cancer, locally advanced prostate cancer Off label: combination therapy for breast cancer, premenopausal ovarian preservation during chemotherapy, breast cancer in male patients, hormone therapy for transgender women		<u>Adult:</u> 3.6 mg SUBQ every 4 weeks	3.6 mg SUBQ every 4 weeks	Women: peripheral edema, vasodilation, acne, diaphoresis, seborrhea, decreased/increased libido, abdominal pain, nausea, infection, depression, asthenia, emotional lability, headache, insomnia Men: hot flashes, abdominal pain, nausea, vasodilation, asthenia, insomnia, decreased libido, fatigue	Decreased bone density, worsening glycemic control, psychiatric side effects, tumor flare, cardiovascular events, gynecomastia	Used for refractory cases due to poor tolerability
Antiandrogens						
Flutamide Metastatic prostate cancer	Inhibits binding of androgen in target tissues	<u>Adult:</u> 250 mg TID with LH agonist	125 to 250 mg TID ³⁷	Hot flashes, diarrhea, galactorrhea, vomiting,	Loss of libido, impotence, gynecomastia,	Liver function monitoring necessary; hepatic toxicity

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Medication/FDA Indication and Off-Label Uses	Mechanism of Action for Priapism	Typical Dose	Dosing Strategies for Priapism	Common Side Effects	Serious Reactions	Caution/Other Information
Digoxin HFrEF, atrial fibrillation, atrial flutter Off label: sustained fetal supraventricular tachyarrhythmia, supraventricular tachycardia (rate control)	Inhibits corporeal smooth muscle Na^+/K^+ pump, leading to inhibition of Ca^{2+} efflux from smooth muscle cells, which promotes contraction and impedes nitric oxide-induced relaxation	<u>Adult:</u> 0.0625 - 0.25 mg once daily <u>Pediatric:</u> - Dosing strategies range by weight from 2.5 mcg/kg BID to 2.5-4 mcg/kg BID - >10 years or >30 kg: 0.125 mg BID or 0.25 mg once daily	0.25 - 0.5 mg daily ³⁵	Bradycardia, dizziness, confusion, weakness, diarrhea, headache	Gynecomastia, decreased libido Toxicity: arrhythmias, hyperkalemia, lethargy, delirium, xanthopsia	Must be monitored; serum target is 0.5 to <0.9 ng/mL, some guidelines go higher; toxicity arises with levels >2 ng/mL Can use every other day dosing strategies in older patients Renally excreted; GFR adjustments necessary Several pertinent interactions
Beta-2 agonist						
Terbutaline Bronchospasm Off label: tocolysis	Relaxes smooth muscle; mechanism of action for priapism poorly understood	<u>Adult:</u> 2.5-5 mg TID; max 15 mg/day <u>Pediatric:</u> - 12-15 years 2.5 mg TID; max 7.5 mg/24 hours - >15 years: 5 mg TID; can reduce to 2.5 mg if side effects; max 15 mg/24 hours	5 to 10 mg immediately, then 5 mg taken 15 minutes later; maintenance dose 5 to 10 mg daily ³¹	Nervousness, tremor, hypertension, sweating, xerostomia, muscle cramps	Shortness of breath, allergic reactions, palpitations, seizures, hypokalemia, hyperglycemia	Contraindicated in patients with diabetes, hypertension, hyperthyroidism, seizures
GABA agonists						
Gabapentin Postherpetic neuralgia, partial seizures Off label: alcohol use disorder, alcohol withdrawal, chronic cough, essential tremor, fibromyalgia, generalized anxiety disorder, hiccups, neuropathic pain, panic disorder, restless leg syndrome, social anxiety disorder, vasomotor symptoms of menopause	Inhibits Ca^{2+} efflux from smooth muscle cells in the corpora, preventing smooth muscle relaxation ⁴²	<u>Adult:</u> 100-300 mg 1-3 times daily to start; max 3600 mg/day <u>Pediatric:</u> - IR, 3 to <12 years: 10-15 mg/kg/day in 3 doses; up to 50 mg/kg/day - >12 years: 300 mg TID; typical 900 to 1800 mg/day; max 2400 mg/day in 3 divided doses	400 mg TID; max 2400 mg daily ⁴³	Dizziness, drowsiness, emotional lability, hostility, ataxia, weight gain	Respiratory depression, anaphylaxis, erectile dysfunction, anorgasmia, DRESS, SJS, TEN, suicidal ideation	Requires renal and hepatic dosing Caution when using concurrently with other CNS depressants due to increased risk of respiratory depression

Medication/FDA Indication and Off-Label Uses	Mechanism of Action for Priapism	Typical Dose	Dosing Strategies for Priapism	Common Side Effects	Serious Reactions	Caution/Other Information
Baclofen Spasticity Off label: alcohol use disorder, hiccups, muscle spasm	Reduces excitatory neurotransmission in presynaptic neurons and inducing inhibitory neurotransmission by GABA agonism; reduction in spasticity can reduce erections	<u>Adult:</u> Oral: 5 to 10 mg TID; max 80 mg/day Intrathecal: 50 mcg; max 100 mcg <u>Pediatric:</u> 12 years+: 5 mg TID; max 80 mg/day Intrathecal: 25 to 50 mcg; max 100 mcg	10 mg TID; increase weekly; max 90 mg ⁴⁴	Dizziness, nausea, vomiting, drowsiness, asthenia, weakness, headache, nausea, constipation, frequent urination	Hallucinations, seizures, potentially addictive; can withdraw if abruptly stopped	Can also be used intrathecally with more efficacy Renal dosing advised; avoid with hemodialysis
Antineoplastic agents						
Hydroxyurea CML, head and neck carcinoma, SCD Off label: AML, differentiation syndrome, essential thrombocytopenia, hypereosinophilic syndrome, meningioma, myelofibrosis, polycythemia vera	Inhibits ribonucleotide diphosphate, arresting cells in S phase; reduces hemolysis and free hemoglobin levels and, therefore, prevents nitric oxide sequestration	<u>Adult:</u> 15 - 100 mg/kg/day ideal body weight; 500 mg to 3 g daily; depending on indication <u>Pediatric:</u> - 6 months to 2 years: 15 to 20 mg/kg/dose - 2 years+: 20 mg/kg/dose once daily	Used as treatment for SCD only	Eczema, headache, constipation, hair loss, weight gain, loss of appetite, changes in skin and nails	Bone marrow suppression, leg ulcers, secondary primary malignancies, infection, macrocytosis, neutropenia, oligospermia	Renally dosed, no need for hepatic dosing Requires dose adjustment in obesity
PDE-5 inhibitors						
Sildenafil ED, PAH Off label: high altitude pulmonary edema, Raynaud phenomenon, sexual dysfunction associated with SSRIs	Chronic use can prevent the downregulation of PDE-5 and chronic accumulation of cGMP, leading to a reduction on priapism episodes	<u>Adult:</u> ED: 50 to 100 mg once daily PAH: 20 mg TID <u>Pediatric:</u> PAH: 10 to 20 mg TID; max 40 mg/dose	25 to 50 mg daily ³⁵	Flushing, diarrhea, dyspepsia, headache, back pain, myalgias, visual disturbance, epistaxis	Hearing loss, hypotension, priapism, visual disturbance	

Medication/FDA Indication and Off-Label Uses	Mechanism of Action for Priapism	Typical Dose	Dosing Strategies for Priapism	Common Side Effects	Serious Reactions	Caution/Other Information
Tadalafil BPH, ED, PAH Off label: high altitude pulmonary edema, sexual dysfunction associated with SSRIs		<u>Adult:</u> ED: 2.5 mg to 10mg daily depending on formulation PAH: 20 to 40 mg once daily <u>Pediatric:</u> Not FDA-approved	5 mg three times weekly ³⁵	Flushing, dyspepsia, nausea, headache, back pain, myalgia, respiratory infections	Hearing loss, hypotension, priapism, visual disturbance	Renal dosing; not recommended for use with severe hepatic impairment

GnRH: gonadotropin releasing hormone

LH: luteinizing hormone

CML: chronic myeloid leukemia

ED: erectile dysfunction

PAH: pulmonary arterial hypertension

BPH: benign prostatic hyperplasia

HRrEF: heart failure with reduced ejection fraction

AML: acute myeloid leukemia

SCD: sickle cell disease

GABA: gamma amino butyric acid

PDE-5: phosphodiesterase 5

SSRI: selective serotonin reuptake inhibitor