

Embryology III

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DRUG-INDUCED INFERTILITY AND SEXUAL DYSFUNCTION



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Categories of fertility-impacting drugs

- Hormone therapy
- Cancer therapy
- Psychotropic medication
- Antihypertensive therapy
- Painkillers
- Antiinfective agents
- Recreational drugs and drug abuse
- Environmental pollutants



Hormone therapy

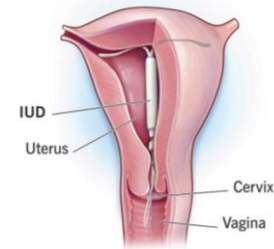
➤ Estrogens + Progesterone

- prevention of ovulation
- reversible birth control (combined contraceptive pill)
- side effect: reduced libido?



➤ Progesterone

- modulation of uterine receptiveness for implantation
- long-acting contraceptives – intrauterine devices (IUD)
- acute administration of high doses interfere with embryo implantation (postcoital/morning) contraceptive pill)



➤ Antiestrogens

- E2 receptor modulators, aromatase inhibitors, GnRH analogues)
- treatment of E2-dependent cancers (breast/ovarian/uterine cancer)
e.g. tamoxifen, clomiphene, anastrozole



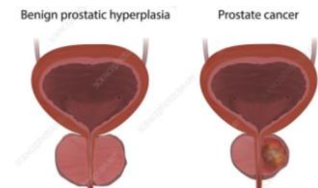
➤ Androgens

- testosterone and its derivatives, anabolic steroids
- treatment of gynecomastia, menorrhagia, mastalgia, endometriosis
- side effect: loss of libido, sexual dysfunction (in males); virilization, hirsutism, anovulation (in females)



➤ Antiandrogens

- treatment of prostatic hyperplasia and cancer, chemical sterilisation; PCOS, hirsutism, seborrhea, acne
- side effects: loss of libido and sexual dysfunction in male



Cancer therapy

- germ cells sensitive to cytotoxic drugs
- acute and long term reproductive toxicity
- impairment of gametogenesis (particularly active spermatogenesis, postnatal oogenesis relatively less sensitive)
- teratogenic affect
- fertility preservation options

Risk level	Medication
High risk (>70%)	<div style="border: 2px solid red; padding: 5px;"> Cyclophosphamide^a Ifosfamide^a Nitrosoureas^a Chlorambucil^a Melphalan^a Busulfan^a Procarbazine^a Temozolomide^a </div> <div style="text-align: right; color: red; font-weight: bold; margin-top: 10px;">Alkylating agents!</div>
Intermediate risk (30%-70%)	Bevacizumab Doxorubicin (as in doxorubicin and cyclophosphamide plus a taxane) FOLFOX regimen (folinic acid, fluorouracil, oxaliplatin ^a) <div style="border: 2px solid red; padding: 2px; display: inline-block;">Cisplatin^a</div>
Low or no risk (<30%)	Methotrexate 5-Fluorouracil Cytarabine Vincristine Bleomycin Doxorubicin (without alkylating agents)

^aAlkylating agents.
 Sources: Lee SJ, et al. *J Clin Oncol.* 2006;24:2917-2931; Loren AW, et al. *J Clin Oncol.* 2013;31:2500-2510; Peccatori FA, et al. *Ann Oncol.* 2013;(24 suppl 6):vi160-vi170; Bedoschi G, et al. *Future Oncol.* 2016;12:2333-2344.

Psychotropic medication

- interaction with neurotransmitters involved in regulation of sexual function (dopamin, serotonin, acetylcholin, adrenalin, noradrenalin)

➤ Antipsychotics (neuroleptics)

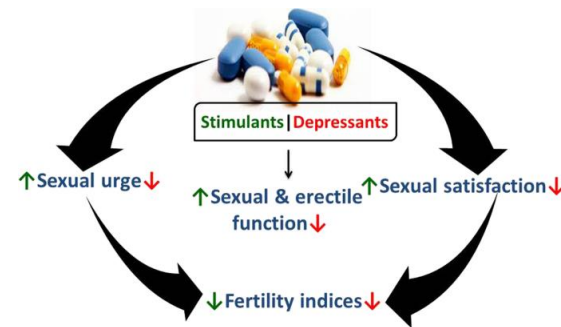
➤ Antidepressants

➤ Lithium

➤ Anxiolytics





➤ Anticonvulsants

- increased level of liver enzymes including SHBP
- reduction of free biactive sexual hormones
- + increased hepatic clearance of of hormones



- hyposexuality, impaired spermatogenesis, loss of libido, erectile dysfunction, delayed/premature ejaculation, ejaculation failure, anorgasmia, amenorrhoea, impotence

Antihypertensive therapy


Antihypertensive Drugs		
Categories of Drugs	Mechanisms	Organs
Central-acting Agents	→ Central attack	→ 
Calcium antagonist β-Blocker	→ Reduction of frequency and power	→ 
RAAS Inhibitor Diuretics β-Blocker	→ Increased fluid excretion	→ 
Vasodilators Calcium antagonists RAAS Inhibitors α-Blocker	→ Vasodilation	→ 

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- antiadrenergic drugs can negatively impact sexual function in men (decreased libido, erection and ejaculation disturbancy, anorgasmia, gynecomastia)
- cardioselective beta-blockers recommended in sexually active men

Cardioselective
(B1 selective) = MANBABB

Metoprolol
Atenolol
Nebivolol
Betaxolol
Acebutolol
Bisoprolol
Esmolol

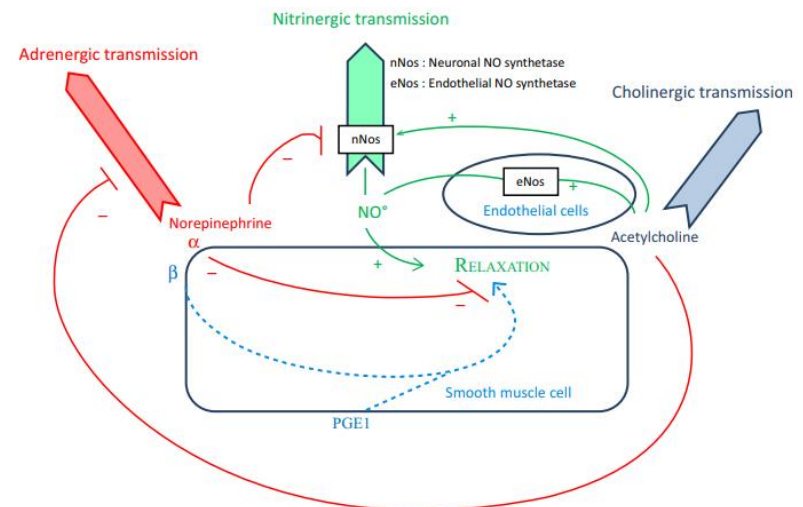


β1
"MANBABB"

Antihypertensive Agents

1	ACE inhibitors (<i>Angiotensin converting enzyme inhibitors</i>)	Enalapril, Lisinopril, Ramipril, Captopril
2	ARBs (<i>Angiotensin receptor blockers</i>)	Telmisartan, Olmesartan, Losartan, Candesartan, Valsartan
3	Calcium channel blockers	Amlodipine, Felodipine, Nimodipine, Nifedipine, Isradipine, Verapamil, Diltiazem
4	Beta blockers	Atenolol, Metoprolol, Bisoprolol, Labetolol, Propranolol,
5	Diuretics	Hydrochlorothiazide, Chlorthiazide, Chlorthalidone, Spironolactone, Furosemide
6	Direct Vasodilators	Hydralazine, Minoxidil, Sodium Nitropruside, Diazoxide
7	Alpha blockers	Terazosin, Doxazosin, Prazosin
8	Central Alpha 2 Agonists	Clonidine, Methyldopa

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Antihypertensive therapy

- maternal hypertension constitutes the risk for placental hypoperfusion, malnutrition and fetal grow restriction
- concern about teratogenic effects of certain drugs
- treatment of chronic/gestational hypertension and preeklapsia
- strict blood pressure control during pregnancy!

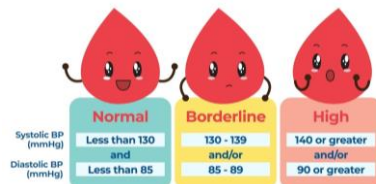


Table 1 Antihypertensive drugs to avoid in pregnancy

Antihypertensive class	Advice	Potential adverse effects	Recommendation
ACE inhibitors	Contraindicated	Teratogenic in the second and third trimester resulting in fetal anuria, oligohydramnios, hypocalvaria, intrauterine growth restriction and patent ductus arteriosus, death	Stop drug ideally before conception or at diagnosis of pregnancy
Angiotensin receptor blockers	Contraindicated	Teratogenic in the second and third trimesters, fetal anuria, oligohydramnios, hypocalvaria, intrauterine growth restriction, patent ductus arteriosus, death	Stop drug ideally before conception or at diagnosis of pregnancy
Diuretics	Avoid	Maternal hypovolaemia, fetal hypoglycaemia, thrombocytopenia, hyponatraemia and hypokalaemia	Use an alternative antihypertensive
Beta blockers (other than labetalol)	Avoid	Fetal bradycardia, intrauterine growth restriction (atenolol)	Use an alternative antihypertensive
Calcium channel antagonists (other than nifedipine and diltiazem)	Avoid	Maternal hypotension and fetal hypoxia	Use an alternative antihypertensive

Table 2 Antihypertensive drugs that can be safely used in pregnancy

Antihypertensive drug*	Class/action	Dose	Adverse effects
Labetalol	Beta blocker	100 mg twice a day - 400 mg three times a day	Bradycardia, bronchospasm, headache
Nifedipine controlled release	Calcium channel antagonist	30 mg daily - 60 mg twice a day	Headache (first-dose effect), flushing, tachycardia, peripheral oedema
Methyldopa	Central action	250 mg twice a day - 750 mg three times a day	Depression, dry mouth, sedation, rarely haemolysis and hepatitis
Hydralazine	Vasodilator	25 mg three times a day - 50 mg three times a day	Flushing, headache, lupus-like syndrome
Prazosin	Alpha blocker	0.5 mg twice a day - 5 mg three times a day	Orthostatic hypotension

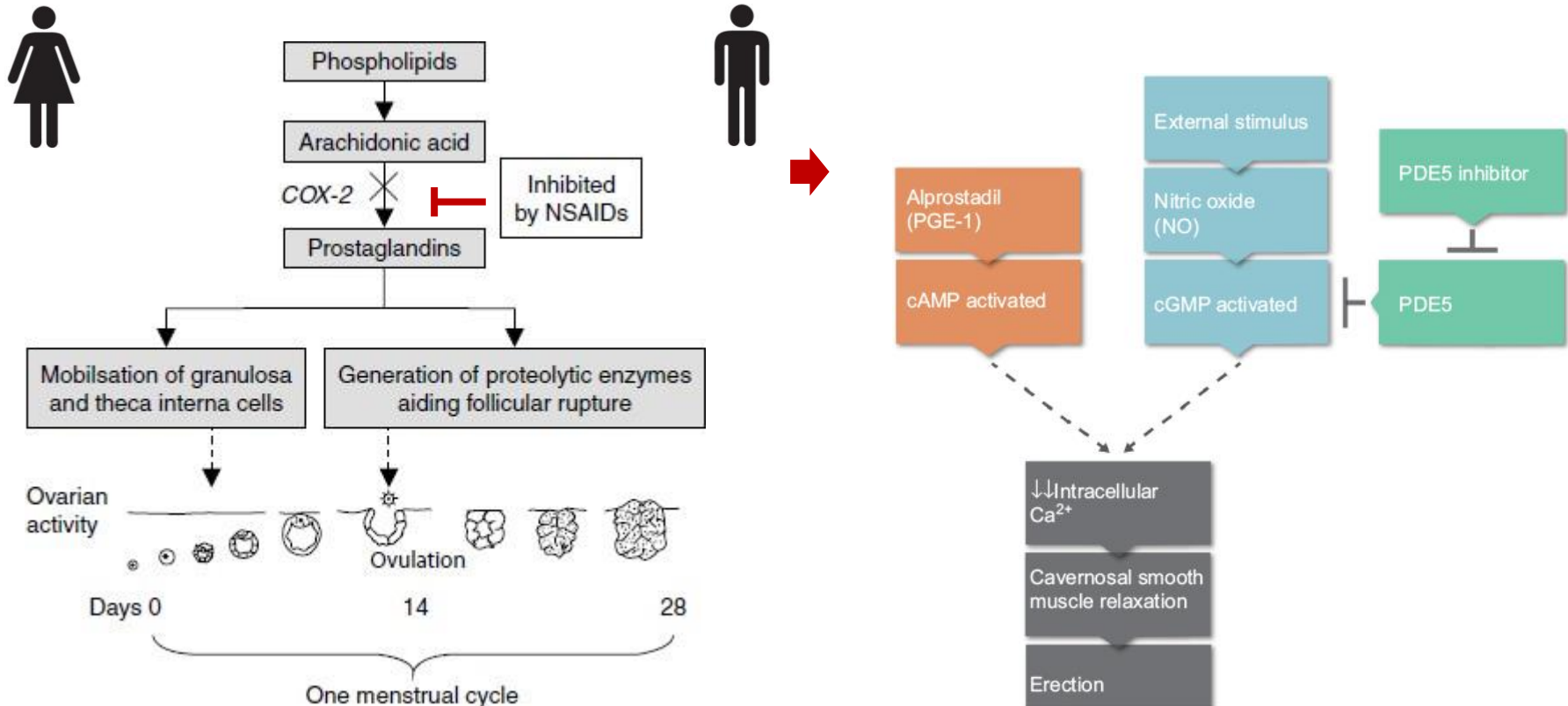
Table 3 Urgent treatment of severe hypertension* in pregnancy

Drug	Dose	Route	Onset of action	Adverse effects
Hydralazine	5-10 mg	Intravenous bolus repeated after 20 min if blood pressure remains >160/110 mmHg	20 min	Flushing, headache, nausea, hypotension, tachycardia
Labetalol	20-80 mg	Intravenous bolus over 2 min, repeat after 10 min if blood pressure remains >160/110mmHg	5 min	Bradycardia, hypotension, fetal bradycardia
Labetalol	200 mg	Oral	30-45 min	Bradycardia, bronchospasm, headache
Nifedipine [†]	10 mg	Oral	30-45 min	Headache, flushing

Painkillers

NSAIDs= non-steroidal anti-inflammatory drugs

- can interfere with ovulation in females and erection and/or ejaculation in males (role of PGE)
- effect on implantation process?



Antiinfective agents

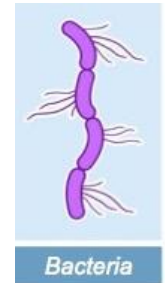
- temporary effects
- treatments of infection recommended



ANTIBIOTICS

- penicillin
- erythromycin
- tetracyclin
- gentamicin
- neomycin
- nitrofurantoin
- suphonamides

- reduction of sperm quality
(oligospermia, asthenospermia, abnormal morphology)



Bacteria

ANTIFUNGAL DRUGS

- ketoconazole

- inhibits Cyp450 and production of androgens
- impairs spermatogenesis



Fungi

ANTIMALARIC DRUGS

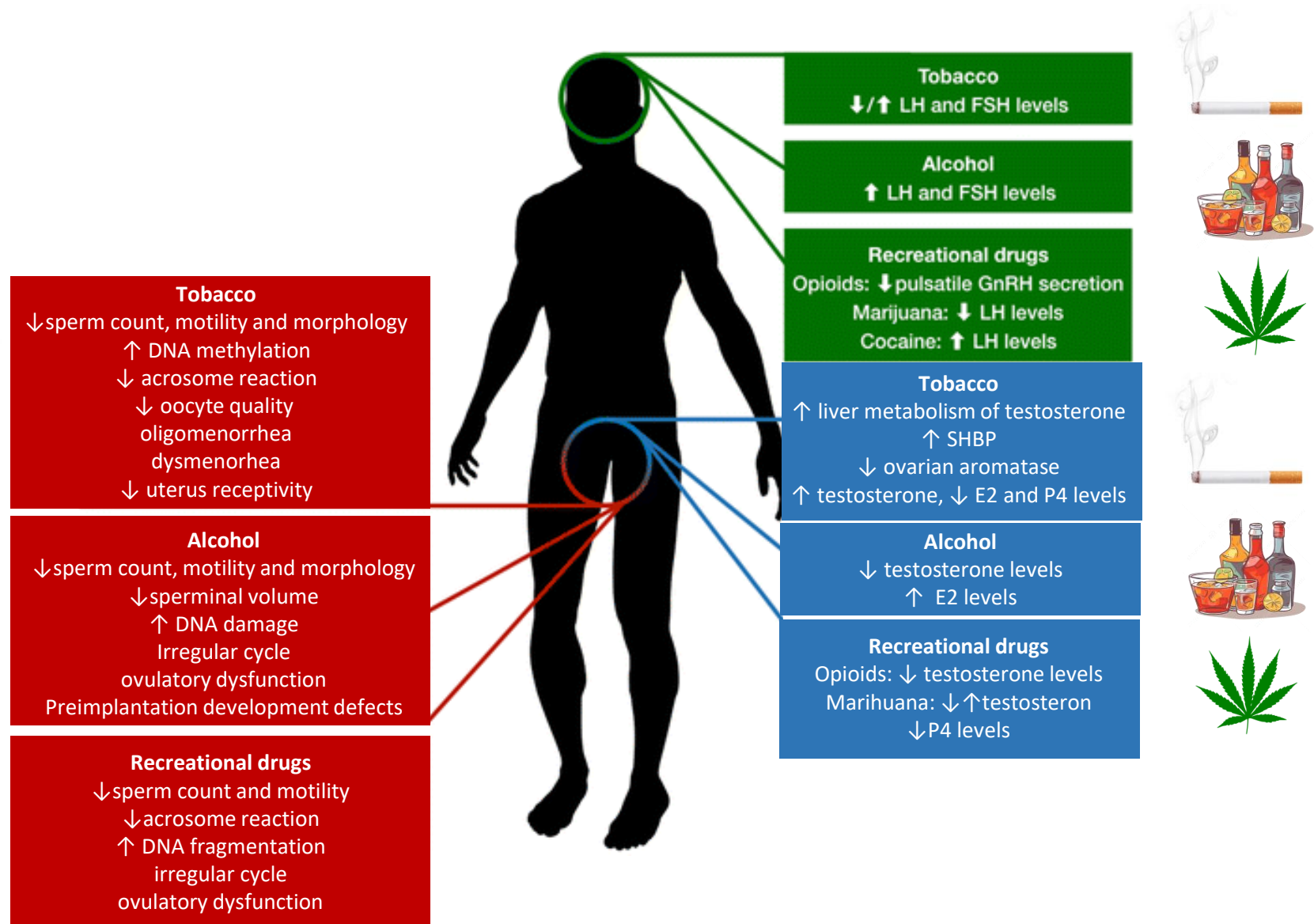
- chloroquine

- ? Prevents acrosomal reaction and reduces sperm fertilization capacity

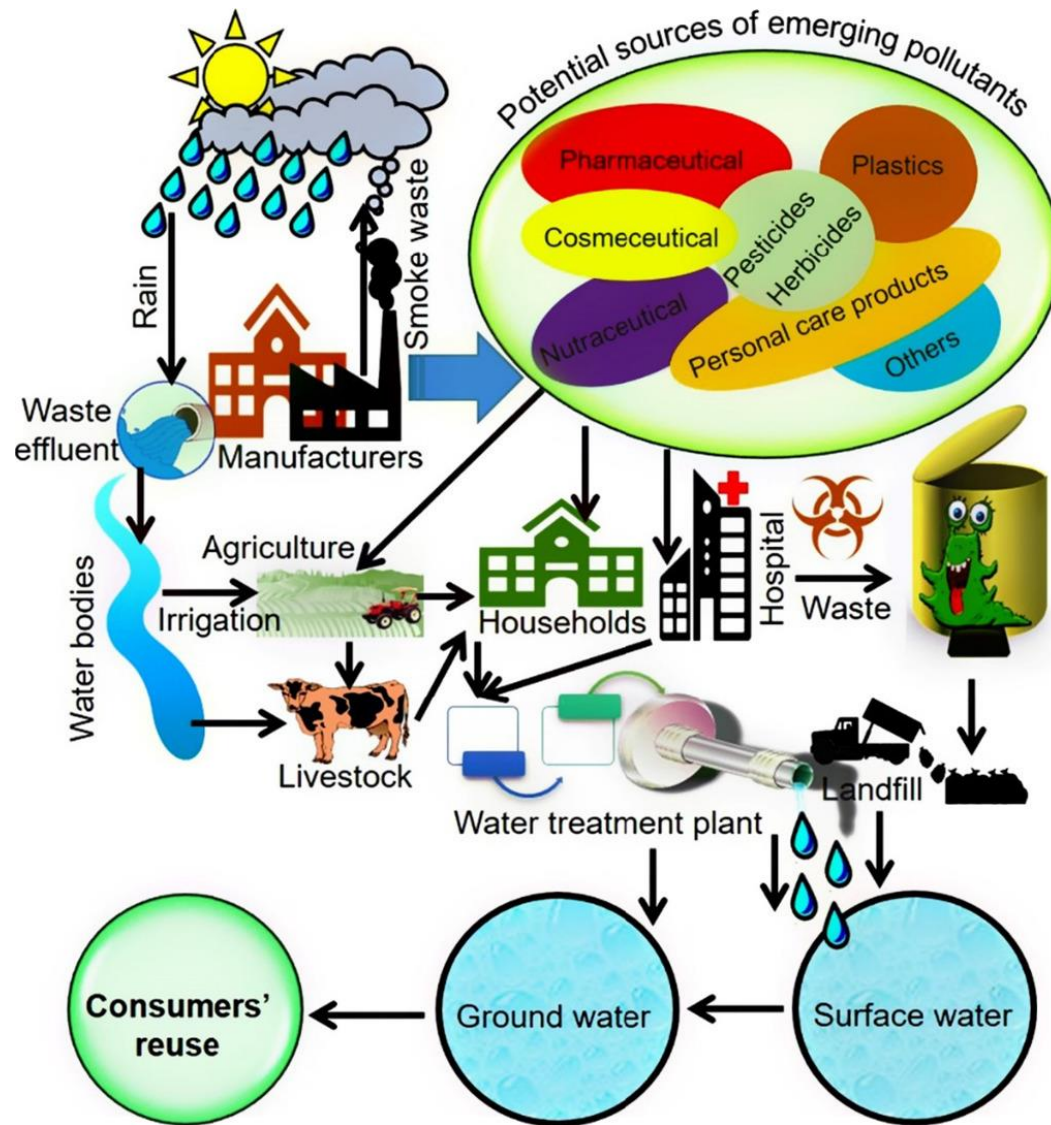


Protozoa

Recreational drugs and drug abuse



Environmental pollutants



Environmental pollutants

