1. **Name**: Trazodone (Desyrel, Desyrel Dividose, Oleptro, Trazodone)

Class: Serotonin-antagonist-and-reuptake-inhibitor (SARIs); antidepressant

MOA: inhibiting both serotonin transporter and serotonin type 2 receptors; inhibits the reuptake of serotonin and blocks the histamine and alpha-1-adrenergic receptors; induces significant changes in 5-HT presynaptic receptor adrenoreceptors

Route: Oral

Indications:

- FDA-approved Uses:
    - antidepressant for treating major depressive disorders
- Non-FDA-approved Uses:
    - induce sedation in patients with sleep problems (not FDA-approved for sleep disorders)
    - Anxiety
    - Alzheimer disease
    - Substance abuse
    - Bulimia
    - Fibromyalgia
    - post-traumatic stress disorder (PTSD)

Contraindications:

- any class of monoamine oxidase inhibitors (MAOIs), including linezolid or intravenous methylene blue
    - MAO inhibitors impair the metabolism of serotonin, and concurrent administration increases serum levels of serotonin

Adverse Reactions:

- increased risk of suicidal thoughts and behaviors in pediatric patients with antidepressant medication use in pediatric patients
- headaches, fatigue, dizziness, and drowsiness/somnolence
- anticholinergic effects (dry mouth), orthostatic hypotension, QT prolongation, torsades, priapism, and an increase in suicidal thoughts
- Visual hallucinations

Monitoring:

- Liver function (baseline and periodically)
- Suicide ideation
- Signs/symptoms of serotonin syndrome
-

Dosing in elderly: It may be administered after meals to decrease lightheadedness and postural hypotension

- The dose in the elderly should be down to 100 mg per day

- serotonergic antidepressants are associated with hyponatremia in elderly patient

Starting and Max doses:

Available doses: 50 mg, 100 mg, 150 mg, and 300 mg in the US

Begin: Evening administration of 75 mg to 150 mg before bedtime (prolonged-release once-a-day administration); may be increased every third day, up to 300 mg per day; dose may be up to 600 mg per day in hospitalized

- FDA-approved Uses:
    - antidepressant for treating major depressive disorders
- Non-FDA-approved Uses:
    - Induce sedation in patients with sleep problems (not FDA-approved for sleep disorders)
        - 50 mg to 100 mg per day of trazodone helped nonorganic insomnia due to depressive disorder
    - Anxiety
    - Alzheimer disease
    - Substance abuse
    - Bulimia
    - Fibromyalgia
    - Obstructive sleep apnea
        - improve apnea and hypopnea episodes; the drug does not worsen hypoxemic episodes
    - Post-traumatic stress disorder (PTSD): if the first-line treatment use of SSRIs does not show efficacy
        - 50 mg to 200 mg
            - demonstrated to reduce episodes of nightmares

References: Shin JJ, Saadabadi A. Trazodone. [Updated 2022 May 2]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470560/

2. **Name**: Apixaban (Eliquis)

Class: Factor Xa Inhibitors

MOA: inhibits platelet activation by selectively and reversibly blocking the active site of factor Xa without requiring a cofactor (eg, antithrombin III) for activity; activation of X to Xa is needed for both intrinsic and extrinsic blood coagluation cascades, blocking this Inhibits free and clot-bound factor Xa, and prothrombinase activity. No direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombi

Route: Oral

Indications:

- Stroke Prophylaxis with Atrial Fibrillation
- Postoperative Prophylaxis of DVT/PE
- DVT or PE Treatment
- Reduce risk of recurrent DVT/PE

Contraindications: Severe hypersensitivity (ie, anaphylactic reactions) and Active pathological bleeding

Adverse Reactions:

Bleeding (Aristotle Study)

- Major (2.13%, warfarin 3.09%; P <0.0001)
- GI (0.83%, warfarin 0.93%)
- Intracranial (0.33%, warfarin 0.82%)
- Intraocular (0.06%, warfarin 0.14%)
- Fatal (0.06%, warfarin 0.24%)
- Clinically relevant nonmajor bleeding (2.08%, warfarin 3.0%; P <0.0001)

Bleeding (Averroes Study)

- Major (1.41%, aspirin 0.92%; P = 0.07)
- Fatal (0.16%, aspirin 0.16%)
- Intracranial (0.34%, aspirin 0.35%)

<1%

- Hypersensitivity reactions (including skin rash and anaphylactic reactions such as allergic edema)
- Syncope

Warnings:

- Increased risk of epidural or spinal hematoma when used with neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture (can result in long-term or permanent paralysis)
- Not recommended for use in patients with triple-positive antiphospholipid syndrome (APS)

Medication interactions:

- Coadministration with strong dual inhibitors of CYP3A4 and P-gp
- Avoid coadministration with strong dual inducers of CYP3A4 and P-gp; such drugs decrease apixaban's systemic exposure
    - Carbamazepine, dexamethasone, phenytoin, rifabutin DECREASE effect of apixaban
- Betrixaban, mifepristone, INCREASE toxicity of apixaban
- Avoid concurrent use with fondaparinux, betrixaban, due to increase anticoagulation

Monitoring:

- Renal impairment for dose adjustment
- Discontinue at least 48 hr before elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding

- Discontinue at least 24 hr before elective surgery or invasive procedures with low risk of unacceptable bleeding or where bleeding would be noncritical in location and easily controlled

Starting and Max doses: Doses: 2.5mg and 5mg

- Stroke Prophylaxis with Atrial Fibrillation
    - 5mg PO BID
        - Serum creatinine ≥1.5 mg/dL: Decrease dose to 2.5 mg BID if patient has 1 additional characteristic of age ≥80 years or weight ≤60 kg
        - ESRD maintained on hemodialysis: 5 mg BID; decrease dose to 2.5 mg BID if 1 additional characteristic of age ≥80 years or weight ≤60 kg is present
- Postoperative Prophylaxis of DVT/PE
    - 2.5mg PO 12-14 hours after surgery
        - Hip replacement: 2.5 mg PO BID for 35 days
        - Knee replacement: 2.5 mg PO BID for 12 days
- DVT or PE Treatment
    - 10mg PO BID x 7 days then 5mg BID x 3-6 months
        - Provoked vs. unprovoked
- Reduce risk of recurrent DVT/PE (Indicated to reduce the risk of recurrent DVT and PE following initial 6 months treatment for DVT and/or PE)
    - 2.5mg PO BID
        - Patient preference/risk factor evaluation

Reference: https://reference.medscape.com/drug/eliquis-apixaban-999805

3. **Name**: Paxlovid (nirmatrelvir/ritonavir)

Class: Antiviral; protease inhibitor

MOA: Nirmatrelvir is a peptidomimetic inhibitor of SARS-CoV-2 main protease (Mpro); Inhibition of SARS-CoV-2 Mpro renders it incapable of processing polyprotein precursors, preventing viral replication. Nirmatrelvir is boosted with low-dose ritonavir that slows nirmatrelvir metabolism via inhibition of CYP3A.

Route: oral

- Dose pack 300 mg nirmatrelvir and 100 mg ritonavir: Each daily blister card contains 4 nirmatrelvir tablets (150-mg) and 2 ritonavir tablets (100-mg)
- Dose pack 150 mg nirmatrelvir and 100 mg ritonavir: Each daily blister card contains 2 nirmatrelvir tablets (150-mg) and 2 ritonavir tablets (100-mg)

Indications:

- EUA (emergency use administration) for:

- Treatment of **mild-to-moderate** coronavirus disease 2019 (COVID-19) in adults and pediatric patients (aged ≥12 years and weight ≥40 kg) testing positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, and who are at **high risk for progression to severe COVID-19**, including hospitalization or death

Contraindications:

- Renal impairment

Medication interactions:

- There are many medication reactions due to Ritonavir being a strong cytochrome P450 (CYP) 3A4 inhibitor and a P-glycoprotein inhibitor
- Strong CYP3A4 inducers may reduce the concentrations of nirmatrelvir and ritonavir, rendering the treatment ineffective
    - Anticancer drugs: Apalutamide
    - Anticonvulsant: Carbamazepine, phenobarbital, primidone, phenytoin
    - Antimycobacterials: Rifampin
    - CFTR modulator: Lumacaftor/ivacaftor
    - Herbal products: St. John's Wort (hypericum perforatum)
- HOLD drugs highly dependent on CYP3A for clearance
    - Alpha1-adrenoreceptor antagonist: Alfuzosin
    - Analgesics: Meperidine
    - Antianginal: Ranolazine
    - Antiarrhythmic: Amiodarone, dronedarone, flecainide, propafenone, quinidine
    - Antigout: Colchicine
    - Antipsychotics: Lurasidone, pimozide, clozapine
    - BPH agents: Silodosin
    - Cardiovascular agents: Eplerenone, ivabradine
    - Ergot derivatives: Dihydroergotamine, ergotamine, methylergonovine
    - HMG-CoA reductase inhibitors: Lovastatin, simvastatin
    - Immunosuppressants: Voclosporin
    - Microsomal triglyceride transfer protein inhibitor: Lomitapide
    - Migraine medications: Eletriptan, ubrogepant
    - Mineralocorticoid receptor antagonists: Finerenone
    - Opioid antagonists: Naloxegol
    - PDE5 inhibitor: Sildenafil (Revatio) when used for pulmonary arterial hypertension (PAH)
    - Sedative/hypnotics: Triazolam, oral midazolam
    - Vasopressin receptor antagonists: Tolvaptan

Prescribe Alternative COVID-19 Therapy

For these medications, management strategies are not possible or feasible, or the risks outweigh the potential benefits.

Anticonvulsants

- Carbamazepine
- Phenobarbital
- Phenytoin
- Primidone

Anti-infective agents

- Glecaprevir/pibrentasvir
- Rifampin
- Rifapentine

Immunosuppressants

- Voclosporin

Cardiovascular agents

- Amiodarone
- Clopidogrel[a,b]
- Disopyramide
- Dofetilide
- Dronedarone
- Eplerenone
- Flecainide
- Ivabradine
- Propafenone
- Quinidine

Neuropsychiatric agents

- Clozapine
- Lumateperone
- Lurasidone
- Midazolam (oral)
- Pimozide

Pain medications

- Meperidine (pethidine)

Pulmonary hypertension medications

- Sildenafil
- Tadalafil
- Vardenafil

Miscellaneous

- Bosentan
- Certain chemotherapeutic agents[c]
- Ergot derivatives
- Lumacaftor/ivacaftor
- St. John's wort
- Tolvaptan

Temporarily Withhold Concomitant Medication, If Clinically Appropriate

Withhold these medications during ritonavir-boosted nirmatrelvir treatment and for at least 2–3 days after treatment completion. They may need to be withheld for longer if the patient is elderly or the medication has a long half-life. If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.

Anticoagulants

- Rivaroxaban[d]

Anti-infective agents

- Erythromycin

BPH medications

- Alfuzosin
- Silodosin

Cardiovascular agents

- Aliskiren
- Ranolazine
- Ticagrelor[b]
- Vorapaxar

Immunosuppressants[f]

- Everolimus
- Sirolimus
- Tacrolimus

Lipid-modifying agents

- Atorvastatin[e]
- Lomitapide
- Lovastatin[e]
- Rosuvastatin[e]
- Simvastatin[e]

Migraine medications

- Eletriptan
- Rimegepant
- Ubrogepant

Neuropsychiatric agents

- Clonazepam[g]
- Clorazepate[g]
- Diazepam[g]
- Estazolam[g]
- Flurazepam[g]
- Suvorexant
- Triazolam[g]

Erectile dysfunction medications

- Avanafil

Respiratory medications

- Salmeterol

Miscellaneous

- Certain chemotherapeutic agents[c]
- Colchicine[h]
- Finerenone
- Flibanserin
- Naloxegol

Adverse Reactions:

1-10%

- Dysgeusia (6%)
- Diarrhea (3%)
- Hypertension (1%)
- Myalgia (1%)

Monitoring:

- Kidney labs (Cr, BUN)
- Liver enzymes
    - Hepatic transaminase elevations, clinical hepatitis, and jaundice reported with ritonavir; caution when administering to patients with preexisting liver diseases, liver enzyme abnormalities, or hepatitis

Dosing in special populations:

Renal impairment

- Mild (eGFR ≥60 to <90 mL/min): No dosage adjustment required
- Moderate (eGFR ≥30 to <60 mL/min): Decrease to 150 mg nirmatrelvir plus 100 mg ritonavir BID x 5 days
- Severe (eGFR <30 mL/min): Not recommended; data are unavailable

Hepatic impairment

- Mild or moderate (Child-Pugh Class A or B): No dosage adjustment required
- Severe (Child-Pugh Class C): Not recommended; data are unavailable

Starting and Max doses:

- Mild-moderate COVID (Initiate as soon as possible after COVID-19 diagnosis and within 5 days of symptom onset)
    - 300 mg nirmatrelvir plus 100 mg ritonavir PO BID x 5 days

References

1. Stader F, Khoo S, Stoeckle M, et al. Stopping lopinavir/ritonavir in COVID-19 patients: duration of the drug interacting effect. J Antimicrob Chemother. 2020;75(10):3084-3086. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32556272.
2. Food and Drug Administration. FDA requiring Boxed Warning updated to improve safe use of benzodiazepine drug class. 2020. Available at: https://www.fda.gov/media/142368/download.

4. **Name**: Oxycodone (Oxycontin, Roxicodone, Xtampza ER, Oxaydo)

Class: opioid analgesic, Schedule II

MOA: Narcotic agonist-analgesic of opiate receptors; inhibits ascending pain pathways, thus altering response to pain; produces analgesia, respiratory depression, and sedation

Route: oral

- Immediate release: 5mg, 7.5mg, 10mg, 15mg, 20mg, 30mg
    - Onset: 10-15 minutes
    - Duration 3-6 hours
- Controlled release: 10mg, 15mg, 20mg, 30mg, 40mg, 60mg, 80mg
    - Duration: <12 hour

Indications:

- Acute moderate to severe pain
- Severe Chronic Pain

Contraindications:

- Known or suspected GI obstruction, including paralytic ileus
- Hypersensitivity (eg, anaphylaxis) to oxycodone
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment

Adverse Effects:

Agitation
Angina pectoris *
Anticholinergic effects (dry mouth, palpitation, tachycardia)
Bradycardia
Cardiac arrest
Coma
Constipation *
Dizziness *
Dysphoria
Euphoria
Faintness
Mental clouding/depression *
Myocardial infarction
Nausea
Nervousness
Pruritus, urticaria
QT-interval prolongation *
Respiratory arrest
Respiratory/circulatory depression
Restlessness
Sedation
Seizures
Severe cardiac arrhythmias *
Shock
ST-segment elevation *
Sweating, flushing, warmness of face/neck/upper thorax
Syncope
Urinary retention, oliguria*
Ventricular tachycardia
Visual disturbances
Vomiting
Weakness*

Warnings:

- Consider prescribing naloxone
    - Based on patient's risk factors for overdose (eg, concomitant use of CNS depressants, a history of opioid use disorder, prior opioid overdose); presence of risk factors should not prevent proper pain management
- Addiction, abuse, and misuse
    - Risk of opioid addiction, abuse, and misuse, which can lead to overdose and death
    - Monitor for respiratory depression, especially during initiation or following a dose increase
- Coadministration with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death

Monitoring:

- Coadministration with other CNS depressants: Initiate long-acting oxycodone with one-third to one-half the recommended starting dose; monitor for signs of respiratory depression, sedation, and hypotension

Medication interactions:

- Alvimopan

Special populations:

Renal impairment

- CrCl <60 mL/min: Serum concentration may increase by 50%; adjust dosage to response

Hepatic impairment

- Reduce dosage in liver disease; decrease dosage of extended-release form to 1/3 or 1/2 of usual starting dosage; titrate to response
- Alternative analgesics are recommended for patients who require a dose of Xtampza ER <9 mg

Starting and Max doses:

Opioid tolerant: those receiving, for 1 week or longer, at least 60 mg/day PO morphine, 25 mcg/hr transdermal fentanyl, 30 mg/day PO oxycodone, 8 mg/day PO hydromorphone, 25 mg/day PO oxymorphone, or an equianalgesic dose of another opioid

- Acute moderate to Severe pain
    - Immediate-release
        - Opioid-tolerant: 10-30 mg PO q4-6hr
        - Opioid-naïve (initial dose): 5-15 mg PO q4-6hr
- Chronic Severe Pain
    - Controlled-release products (OxyContin, Xtampza ER)
        - Oxycontin
            - Opioid naïve: 10 mg PO q12hr initially
                - Can titrate gradually every 1-2 days, increasing by 25-50% increments, with q12hr dosing interval maintained
                    - A single dose >40 mg ER or total dose >80 mg ER only done in opioid-tolerant patients
        - Xtampza ER
            - Opioid-naïve patients: 9 mg PO q12hr with food

Reference: https://reference.medscape.com/drug/oxycontin-xtampza-er-oxycodone-343321

5. **Name**: Hydromorphone(Dilaudid, Dilaudid-HP, Exalgo)

Class: opioid analgesic, Schedule II

MOA: Mu-opioid receptor agonist; inhibits ascending pain pathways, thus altering response to pain; main therapeutic action is analgesia;

Route: PO, SC, IM, IV

PO: 2mg, 4mg, 8mg, 5mg/5mL

ER: 8mg, 12mg, 16mg, 32mg

Injection: 1mg/mL, 2mg/mL, 4mg/mL, 10mg/mL

Suppository: 3mg

Indications:

- Acute Moderate to Severe Pain
- Chronic Severe Pain

Off-label uses:

- Cough

Contraindications:

- Hypersensitivity
- Obstetrical analgesia
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected gastrointestinal obstruction, including paralytic ileus
- Hypersensitivity to hydromorphone, hydromorphone salts, any other components of the product, or sulfite-containing medications (e.g., anaphylaxis)
- Increased intracranial pressure resulting from intracranial lesion; conditions resulting in depressed ventilatory function including COPD, emphysema, status asthmaticus, kyphoscoliosis, cor pulmonale
- Paralytic ileus, opioid nontolerant patients, known ro suspected pre-existing GI surgery or diseases resulting in narrowing of GI tract loops in the GI tract or GI obstruction

Adverse Reactions:

- Anticholinergic: Dry mouth, palpitation, tachycardia, urinary retention
- Cardiovascular: Angina pectoris, bradycardia, cardiac arrest, circulatory depression, myocardial infarction, QT-interval prolongation, severe cardiac arrhythmias, shock, ST-segment elevation, syncope, ventricular tachycardia
- Central nervous system (CNS): Agitation, coma, dizziness, dysphoria, mental clouding or depression, euphoria, faintness, nervousness, restlessness, sedation, seizures, visual disturbances, weakness
- Gastrointestinal (GI): Constipation, nausea, vomiting, anorexia, abdominal distention, bilieary tract spasm, decreased appetite, decreased intestinal motility, gastroesophageal reflux disease, paralytic ileus,
- Respiratory: Respiratory depression, respiratory arrest, hypoxia, bronchospasm, dyspnea, rhinorrhea, flu-like symptoms (Exalgo)
- Other: Flushing, pruritus, sweating, urticaria, skin rash, hyperhidrosis, warmness of face/neck/upper thorax

Warnings:

- Schedule II opioid agonists (eg, morphine, oxymorphone, oxycodone, fentanyl, methadone) have highest potential for abuse and risk of producing respiratory depression

- Long-term opioid use may cause secondary hypogonadism, which may lead to sexual dysfunction, infertility, mood disorders, and osteoporosis
- Controlled-release formulation should only be used when continuous analgesia is required over an extended period of time; not for use PRN
- Profound sedation, respiratory depression, coma, and death may result from concomitant use with benzodiazepines or other CNS depressants; because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate; if decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe lowest effective dosages and minimum durations of concomitant use; if concomitant use is warranted, consider prescribing naloxone for emergency treatment of opioid overdose
- Profound sedation, respiratory depression, coma, and death may result from concomitant use with benzodiazepines or other CNS depressants; because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate; if decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe lowest effective dosages and minimum durations of concomitant use; if concomitant use is warranted, consider prescribing naloxone for emergency treatment of opioid overdose

Starting and Max doses:

*** Oral dose: Initiate at low end of dosage range; consider lowering dose by 25-50% in patients >70 years

- Acute Moderate to Severe Pain
    - PO
        - Immediate-release: 2-4 mg q4-6hr PRN; a gradual increase in dose may be required
        - Oral liquid (usual dose): 2.5-10mg (2.5=10ml) q3-6hr PRN
    - SC/IM
        - 1-2 mg q2-3hr PRN; adjust dose according to pain and adverse effects
            - IM dose not recommended for use as it may result in variable absorption and lag time to peak effect
    - IV
        - Opioid naive: 0.2-1 mg IV q2-3hr PRN; may require higher doses in patients with prior opioid exposure
        - Critically ill patients (opiate-naive patients): 0.2-0.6 mg q1-2hr PRN given slowly over 2-3 minutes; patients with previous opiate exposure may tolerate higher doses
            - Continuous infusion: 0.5-3 mg/hr, titrated to response
    - Patient-controlled analgesia
        - Usual concentration, 0.2 mg/mL; demand dose, 0.1-0.2 mg; dose range is 0.05-0.4 mg
            - Lockout interval: 5-10 minutes
    - Rectal
        - 3 mg PR q6-8hr

- Chronic Severe Pain
    - Long-acting (Exalgo) is indicated for the management of pain in opioid tolerant patients severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
        - 8-64 mg PO qDay
            - May administer a starting dose equivalent to patient's total daily oral hydromorphone dose administered once daily with or without food
            - increase dose no more frequently than q3-4days
            - May titrate with increases of 25-50% of current daily dose
            - Consider increasing dose if more than 2 doses of rescue medications are needed within 24hr within 2 consecutive days
- Cough
    - 1 mg PO q3-4hr PRN

References: https://reference.medscape.com/drug/dilaudid-hydromorphone-343313