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Clomipramine

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Continuing Education Activity

The only FDA-approved use for clomipramine is to treat obsessive-compulsive disorder (OCD) in ages ten and older. For the treatment of OCD, clomipramine was found to be more effective than sertraline, fluoxetine, and fluvoxamine in a meta-analysis. Clomipramine is used off-label to treat patients with depression, anxiety, treatment-resistant depression, cataplexy syndrome, insomnia, neuropathic pain, chronic pain, body dysmorphic disorder, panic disorder, premature ejaculation, pediatric nocturnal enuresis, and trichotillomania. This activity reviews indications, mechanism of action, administration, contraindications, monitoring, and toxicity associated with clomipramine and the interprofessional team's role in caring for patients with conditions that indicate therapy with clomipramine.

Objectives:

- Identify the indications for initiating clomipramine therapy.
- Describe the mechanism of action of clomipramine.
- Review the contraindications for clomipramine therapy.
- Outline the importance of improving care coordination among interprofessional team members to improve outcomes for patients receiving therapy with clomipramine.

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Indications

The only FDA-approved use for clomipramine is the treatment of obsessive-compulsive disorder (OCD) in ages ten and older.[1][2] Clomipramine was the first FDA-approved medication for OCD in 1989. For the treatment of OCD, a meta-analysis found clomipramine was more effective than sertraline, fluoxetine, and fluvoxamine.[3][4] The researchers found clomipramine improved Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) by 37% in children and adolescents.[2]

Clomipramine is used off-label to treat patients with the following conditions:

- Depression[5]
- Anxiety[6]
- Treatment-resistant depression[7]
- Cataplexy syndrome[8]
- Insomnia[8]

- Neuropathic pain[7]
- Chronic pain[7]
- Body dysmorphic disorder[9]
- Panic disorder[9]
- Premature ejaculation[10]
- Pediatric nocturnal enuresis[10]
- Trichotillomania[11]

Researchers conducted a meta-analysis examining the relative effectiveness in treating OCD between clomipramine, sertraline, fluvoxamine, and fluoxetine; clomipramine demonstrated the greatest effectiveness.[4]

Mechanism of Action

Clomipramine is a tertiary amine belonging to the class of medications known as tricyclic antidepressants (TCA). It is a dibenzazepine TCA. Clomipramine is a serotonin reuptake inhibitor (S-RI) with a stronger affinity for the serotonin transporter (SERT) than other TCAs and S-RIs.[2] The resulting action of clomipramine increases serotonergic and noradrenergic transmission.[2]

Metabolism of clomipramine is primarily through the liver via oxidation by CYP450 2D6. The half-life of clomipramine is 17 to 28 hours. Clomipramine is then metabolized to the steady-state active metabolite desmethyl clomipramine by CYP450 1A2.[12] Desmethyl clomipramine has more noradrenergic activity than serotonergic.[12] Experts often use fluvoxamine, a CYP450 1A2 inhibitor, with clomipramine in treatment-resistant OCD.[13] By adding the CYP450 1A2 inhibitor, the conversion from clomipramine to desmethyl clomipramine is blocked, resulting in an increase in serotonergic activity.[13]

Administration

Clomipramine is available in generic formulations.

Clomipramine is routinely administered orally, per os (PO), although open trials have taken place with intravenous (IV) clomipramine in treatment-resistant OCD.[14][15][16] Clomipramine is available in capsule form as a hydrochloride salt, with dosages of 25 mg, 50 mg, and 75 mg.

The initial dose for adults and children is 25 mg per day. The dose is titrated in increments of 25 mg per day every 4 to 7 days to a target dose between 100 mg to 250 mg per day, with a max dose in the first week of 100 mg per day the first two weeks. For children (aged ten and older) and adolescents, the typical daily dose is 1 to 3 mg per kg. The maximum daily dose for both children and adults is 250 mg per day. Prescribers may give clomipramine in single or split doses, with the largest dose given at bedtime due to sedation risk. Due to gastrointestinal side effects, patients may take it with meals, although absorption is not affected by food. Patients with trouble swallowing can open the capsules and mix the contents with soft foods such as applesauce or pudding (swallow the mixture without chewing).

For off-label indications, the dosing is between 25 and 100 mg at bedtime, with variations depending on the specific indication.

The onset of action of clomipramine is usually between 6 to 12 weeks for OCD; it may treat anxiety or insomnia immediately. If the patient achieves OCD remission with clomipramine, treatment should continue indefinitely.[17][14] There have only been a few long-term studies for clomipramine.[17] Long-term OCD studies reveal a low remission rate, with one study noting 20% at 40 years.[17] A later study noted that 40 to 60% of individuals given a trial of SRIs respond to treatment.

For non-responders or those with side effects, clomipramine may require discontinuation; to taper clomipramine, reduce the dose by 50% every three days until reaching the lowest dose of 25 mg per day and then discontinue.[2] Abrupt discontinuation of clomipramine can result in patients experiencing withdrawal symptoms of dizziness, irritability, headache, vivid dreams, and flu-like symptoms.[2]

Prescribers often augment clomipramine therapy with buspirone, lithium, atypical antipsychotics, or fluvoxamine for OCD.[2]

Adverse Effects

The adverse effects of clomipramine include nausea, weight gain, increased appetite, sedation, dry mouth, constipation, urinary retention, blurred vision, headache, dizziness, fatigue, hypotension, anxiety, restlessness, sweating, blue-green urine, and sexual dysfunction.[2]

Life-threatening adverse effects include arrhythmia, tachycardia, QTc prolongation, orthostasis, seizures, paralytic ileus, hyperthermia, hepatic failure, increased intraocular pressure, mania induction, and activation of suicidality.[2][18]

Adverse effects of clomipramine have been found in fetuses, as the medication crosses the placenta.[19] Lethargy, congenital heart defects, and withdrawal have occurred in infants born to mothers taking clomipramine during pregnancy.[19][20] Clomipramine may also be present in breast milk; therefore, it is recommended to bottle feed or discontinue the medication if the risk outweighs the benefits.[21] If the benefits outweigh the risk, clomipramine therapy may continue during pregnancy and breastfeeding.

Contraindications

Clomipramine is contraindicated in patients taking monoamine oxidase inhibitors (MAOI) or CYP450 2D6 inhibitors. Clomipramine therapy may not initiate until at least 14 days after discontinuation of the MAO. Other S-RIs or MAOIs may be added or started two weeks after discontinuation of clomipramine. CYP450 2D6 inhibitors may result in increased drug levels of clomipramine. Initiating clomipramine is contraindicated while being treated with linezolid or IV methylene blue, nor can it be started during the acute phase after myocardial infarction. Other contraindications to clomipramine include patients with any degree of heart block, prolonged QTc interval, arrhythmia, acute heart failure, mania, liver disease, narrow-angle glaucoma, urinary retention, or allergy to clomipramine.[2]

Monitoring

Due to the risk of QTc prolongation and arrhythmia, electrocardiogram (EKG) testing is a recommendation at baseline and after reaching therapeutic effect.[2] Due to the risk of metabolic adverse effects, weight, body mass index (BMI), fasting plasma glucose, and fasting lipids are recommended at baseline and during treatment. In patients with a risk of electrolyte imbalances, a basic metabolic panel (BMP), in addition to magnesium, should be obtained at baseline and during treatment. In 7% of the population, a phenotypic variant of CYP450 2D6 is present; therefore, dose reduction or phenotypic testing may be options.[22] These phenotypic variants can result in a 40-fold difference in clomipramine concentrations. In children and adolescents, the clinician should monitor for growth, activation of mania in bipolar disorder, and the emergence of suicidality.

Toxicity

Toxicity with clomipramine is often associated with doses over 300 mg per day.[2] Toxicity with clomipramine can occur in overdose or if a patient is taking MAOI, S-RI, or drugs that inhibit CYP450 2D6. The most common symptoms seen in toxicity are arrhythmias, seizures, and hypotension. Coma and death may also occur in severe overdoses. The antidote for TCAs is IV sodium bicarbonate (NaHCO3), along with supportive care of vital signs.

Clomipramine, combined with S-RI, MAOI, or other serotonergic medications, may result in serotonin syndrome, with

a triad of altered mental status, myoclonus, and autonomic hyperactivity. The antidote in serotonin syndrome is cyproheptadine, along with supportive care of vital signs.

Enhancing Healthcare Team Outcomes

Healthcare providers should monitor patients on clomipramine for metabolic effects and cardiac abnormalities by obtaining weight, BMI, fasting glucose, fasting lipid panel, BMP, magnesium, and EKG at baseline and routinely during treatment.[2] Providers, including all clinicians (MDs, DOs, NPs, PAs), specialists, and pharmacists and nurses with specialty training in psychiatric health, should also monitor for risk of mania induction or suicidality as part of an interprofessional team approach to care.

If patients on clomipramine experience adverse effects, the medication regimen should be titrated down, discontinued, or the patient referred to a psychiatrist or mental health nurse. A pharmacy consult is necessary for potential interactions and to verify dosing, making recommendations to the team as needed. The treatment outcomes for clomipramine in OCD are superior to S-RIs, but adverse effects limit medication tolerability; this is why an interprofessional team collaborating across disciplines can optimize the therapeutic benefits of clomipramine while minimizing adverse effects.[2] [Level 5]

Review Questions

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