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Q: What is clomipramine?

A: Clomipramine, or clomipramine hydrochloride, is a tricyclic antidepressant (TCA) with U.S. Food and Drug Administration (FDA) approval for the treatment of obsessive-compulsive disorder (OCD; FDA, 2001). First studied in the 1960s, clomipramine was approved under the brand name Anafranil in 1989 and is available in generic form.

Q: What are the potential mechanisms of action underlying clomipramine for OCD?

A: Symptom relief in OCD patients treated with clomipramine contributed to understanding OCD as a disorder of serotonergic dysfunction (Fineberg & Brown, 2011; Dougherty et al., 2018). Clomipramine acts by blocking reuptake of serotonin and increasing the amount of serotonin available in the brain. Neuroimaging studies of regional serotonin (5-HT) abnormalities in patients with OCD (Graat, Figeo, & Denys, 2017) provide some evidence that reduced serotonin is implicated in OCD but it is likely that additional neurotransmitter systems are also involved (Dougherty et al., 2018).

Q: Is clomipramine recommended as a treatment for OCD in the Military Health System (MHS)?

A: There is no VA/DoD clinical practice guideline (CPG) on the treatment of obsessive-compulsive disorder. *The MHS relies on the VA/DoD CPGs to inform best clinical practices. In the absence of an official VA/DoD recommendation, clinicians should look to CPGs and authoritative reviews published by other recognized organizations and may rely on knowledge of the literature and clinical judgement.*

Q: Do other authoritative reviews recommend clomipramine as a treatment for OCD?

A: Yes. CPGs and authoritative reviews published by other organizations recommend the use of clomipramine for OCD.

Other recognized organizations publish CPGs or conduct systematic reviews and evidence syntheses on psychological health topics using grading systems similar to the VA/DoD CPGs. These include the American Psychiatric Association, American Psychological Association, and the United Kingdom's National Institute for Health and Care Excellence. Additionally, Cochrane is an international network that conducts high-quality reviews of healthcare interventions.

- The American Psychiatric Association's (APA) Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder states that clomipramine is a recommended pharmacological agent, with a Level I rating ("recommended with substantial clinical confidence") but goes on to state that a selective serotonin reuptake inhibitor (SSRI) is preferred for a first medication trial due to its "less troublesome side effect profile" (APA, 2007).
- The United Kingdom's National Institute for Health and Care Excellence (NICE) states that "clomipramine should be considered in the treatment of adults with OCD...after an adequate trial of

at least one SSRI has been ineffective or poorly tolerated, if the patient prefers clomipramine or has had a previous good response to it,” (NICE, 2005, p. 25).

Q: Is there any recent research on clomipramine as a treatment for OCD?

A: The efficacy of clomipramine in reducing obsessive thoughts and compulsive behaviors is well-established (Piccinelli et al., 1995; Ackerman & Greenland, 2002; Fineberg & Gale, 2005; Skapinakis et al., 2016). A recent systematic review aimed to provide a comprehensive overview of the efficacy of pharmacological interventions for OCD (Del Casale et al., 2019). The authors included 177 articles, including experimental studies, pharmacological trials, and systematic reviews and meta-analyses. With regards to clomipramine, they found consistent evidence of its efficacy. Some studies indicated that it was slightly better than selective serotonin reuptake inhibitors (SSRIs), while others found them to be of equivalent efficacy. SSRIs are a preferred treatment due to their more favorable side effect profile. There was also some evidence that SSRIs augmented with clomipramine were effective for treatment-resistant OCD (Del Casale et al., 2019). Bandelow et al. (2023) reported similar results in version 3 of the World Federation of Societies of Biological Psychiatry (WFSBP), a multi-country effort to develop practice recommendations based on published randomized, controlled trials. The WFSBP noted the long-standing evidence of the efficacy of clomipramine and the preference for SSRIs due to the side effect profile. They found insufficient evidence of superiority to SSRIs. Finally, clomipramine outperformed placebo in long-term and relapse prevention studies.

Q: What conclusions can be drawn about the use of clomipramine as a treatment for OCD in the MHS?

A: Clomipramine is an effective treatment for OCD. Efficacy comparisons to SSRIs indicate that clomipramine is equivalent or slightly superior. SSRIs are the preferred treatment due to their similar efficacy and superior safety and tolerability. As with other TCAs, there is risk of fatal cardiac arrest with overdose of clomipramine. Augmenting SSRIs with clomipramine may assist with treatment-resistant OCD. Further research is needed to determine the comparative effectiveness of pharmacological treatments, psychotherapies, and combination treatments for OCD.

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