

Clomipramine for Obsessive-Compulsive Disorder

Q. What is clomipramine?

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

Q. What are the potential mechanisms of action underlying clomipramine?

A. Symptom relief in OCD patients treated with clomipramine led to the understanding of OCD as a disorder of serotonergic dysfunction (Fineberg & Brown, 2011; Dougherty et al., 2018). Clomipramine acts by blocking reuptake of serotonin. There is some evidence from neuroimaging studies of regional serotonin (5-HT) abnormalities in OCD (Graat, Figeet, & Denys, 2017) that reduced serotonin within brain circuits is implicated in OCD (Dougherty et al., 2018). However, it is likely that additional neurotransmitter systems also are involved in OCD (Dougherty et al., 2018). Clomipramine works by inhibiting the reuptake of serotonin from the synapses and increasing the amount of serotonin available in the brain.

Q. Is clomipramine recommended as a front-line treatment for OCD in the Military Health System (MHS)?

A. There is no VA/DoD clinical practice guideline (CPG) on the treatment of OCD.

The MHS relies on the VA/DoD clinical practice guidelines (CPGs) to inform best clinical practices. However, in the absence of an official VA/DoD recommendation, clinicians should look to CPGs published by other recognized organizations, and may rely on knowledge of the literature and clinical judgement.

Q. Do other organizations with CPGs for the treatment of OCD recommend clomipramine?

A. **Yes.** CPGs published by other organizations recommend the use of clomipramine as a second-line pharmacotherapy for OCD.

- The American Psychiatric Association's Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder states that clomipramine is a recommended pharmacological agent, with a Level I ("recommended with substantial clinical confidence") rating, 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" (American Psychiatric Association, 2007).
- The Canadian Psychiatric Association rates the level of evidence as "1" for clomipramine, but states that clomipramine should be considered when two different first-line agents (selective serotonin reuptake inhibitors [SSRIs]) have not produced the expected benefit, due to concerns of safety and tolerability (Canadian Psychiatric Association, 2006).
- 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)."

Q. Do other authoritative reviews recommend clomipramine as a front-line treatment for OCD?

A. **No.** Other authoritative reviews have not substantiated the use of clomipramine for OCD.

Several other recognized organizations conduct systematic reviews and evidence syntheses on psychological health topics using similar grading systems as the VA/DoD CPGs. These include the Agency for Healthcare Research and Quality (AHRQ) and Cochrane.

- AHRQ: No reports on OCD were identified.
- Cochrane: No systematic reviews of clomipramine for OCD were identified.

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

A. The efficacy of clomipramine in reducing obsessive and compulsive behaviors has been well established for decades (Piccinelli, Pini, Bellantuono, & Wilkinson, 1995; Greist, Jefferson, Kobak, Katzelnick, & Serlin, 1995; Stein, Spadaccini, & Hollander, 1995). However, findings on the comparative efficacy of clomipramine versus SSRIs are mixed. Meta-analytic reviews have concluded that clomipramine is more efficacious than SSRIs (Greist et al., 1995), even after controlling for heterogeneity across studies (Ackerman & Greenland, 2002). However, direct comparisons from head-to-head trials have found no significant difference in efficacy between clomipramine and SSRIs, which demonstrate superior safety and tolerability (Zohar & Judge, 1996; Mundo, Rouillon, Figuera, & Stigler, 2001; Bisserbe, Lane, & Flament, 1997; Fineberg & Gale, 2005). A recent systematic review and network meta-analysis of pharmacological and psychotherapeutic interventions for OCD found that there were no significant differences between clomipramine and SSRIs on OCD symptom severity (Skapinakis et al., 2016).

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

A. Though the efficacy of clomipramine for reducing symptoms of OCD is well established, SSRIs should be considered front-line pharmacotherapy for OCD, 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. Treatment guidelines indicate that clomipramine may be considered as a second-line pharmacotherapy. Further research is needed to determine the comparative effectiveness of pharmacological treatments, psychotherapies, and combination treatments for OCD. Treatment decisions should take into account practical considerations such as availability and patient preference that might influence treatment engagement and retention.

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