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Efficacy and safety of parenteral clomipramine compared to oral clomipramine or other treatments for depression or obsessive-compulsive disorder

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SAHLGRENSKA UNIVERSITETSSJUKHUSET VGR

Efficacy and safety of parenteral clomipramine compared to oral clomipramine or other treatments for depression or obsessive-compulsive disorder [Effekt och säkerhet för parenteral klomipraminbehandling vid depression respektive tvångssyndrom]

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Ylva Carlsson
Head of HTA-centrum of Region Västra Götaland, Sweden, 2025-07-02

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1 Abstract

Background: In severe cases of depression and obsessive-compulsive disorder (OCD), the tricyclic antidepressant clomipramine is sometimes administered parenterally, especially in treatment-resistant conditions and inpatient care. Arguments for parenteral compared to oral administration include a more predictable bioavailability, a higher parent to metabolite ratio with serotonergic activity being more pronounced in the parent drug, reaching steady state faster, reduced compliance problems, and a potential placebo effect related to the administration.

Question at issue: In patients with depression or OCD, is parenteral administration of clomipramine superior to oral clomipramine, other treatments, or placebo in terms of reducing depressive symptoms and OCD symptoms within two weeks, as well as other important outcome measures?

Methods: Two authors performed literature searches (September 2024) in Medline, Embase, the Cochrane Library and PsycInfo. They independently assessed the abstracts and, in consensus, selected full-text articles that were not clearly out of scope to be sent to the other authors, who then decided in consensus whether the inclusion criteria were fulfilled, i.e., whether information regarding the question at issue was provided. The included studies were critically appraised, and data were extracted. Studies without a high risk of bias formed the primary basis for the conclusions. Meta-analyses were performed when applicable. Certainty of evidence was assessed according to GRADE. The study protocol was preregistered with PROSPERO (CRD420250654029).

Results: Fourteen randomised controlled trials (RCTs) including a total of 418 patients fulfilled the inclusion criteria, whereof ten were assessed not to have a high risk of bias. No RCTs compared parenteral clomipramine with the beforehand determined relevant comparisons electroconvulsive therapy (ECT) and ketamine. No RCTs provided information regarding the outcomes suicide attempts, all-cause mortality, suicidal ideation, global functioning, length of hospital stay, or health-related quality of life.

Depression
For the comparison of ***intravenous versus oral clomipramine***, five double-blind RCTs (n=170) formed the basis for the conclusion. Results from three RCTs could be pooled, resulting in a mean difference of change in Hamilton depression rating scale (HDRS) scores of -1.27 (95% confidence interval (CI): -3.09 to 0.54; minimum clinically important difference: 2). Thus, intravenous clomipramine may not be superior to oral administration in terms of reducing depressive symptoms within two weeks, but a clinically relevant effect cannot be excluded (low certainty of evidence). Further, there may be no difference regarding change in HDRS scores after more than two weeks and treatment discontinuation. Regarding adverse events related to administration via injection or infusion, no conclusions could be drawn based on available RCTs, but infusion-related adverse event rates like thrombophlebitis and hypotension occurred and were in line with rates described in the summary of product characteristics. For the comparison of ***intravenous clomipramine versus other treatments***, the available RCTs did not allow for conclusions, or no RCTs were available. For the comparison of ***intravenous clomipramine versus placebo***, one double-blind RCT (n=16; mean difference of change in HDRS scores: -6.0 (95% CI: -0.9 to -11) formed the basis for the conclusion that intravenous clomipramine may be superior to placebo in terms of reducing depressive symptoms within two weeks (low certainty of evidence; this assessment does not concern the efficacy of clomipramine as an active substance).

Obesessive-compulsive disorder
For the comparison of ***intravenous versus oral clomipramine***, no conclusion could be drawn based on available RCTs (very low certainty of evidence). For the comparison of ***intravenous clomipramine versus other treatments***, no RCTs were available. For the comparison of ***intravenous clomipramine versus placebo in patients with OCD***, one double-blind RCT (54 patients poorly responsive to oral clomipramine; mean difference of change in Yale-Brown obsessive compulsive scale scores: -2.5 (95% CI: -5.6 to 0.6; minimum clinically important difference: 4.9)) formed the basis for the conclusion that in patients with OCD refractory to oral clomipramine, intravenous clomipramine may not be superior to placebo regarding effects on OCD symptoms at two weeks, but a clinically relevant effect cannot be excluded (low certainty of evidence).

Economic aspects: As available evidence only allows conclusions based on low certainty evidence for some of the critical and important outcomes, and no evidence is available for the predefined relevant comparisons ECT and ketamine, costs calculations were restricted to drug costs. During the first week of treatment, i.e., the week where the costs differ as the patients thereafter receive oral treatment, the drug cost of parenteral clomipramine vary between 3,670 and 10,190 SEK depending on administration protocol, whereas the cost of oral clomipramine is 43 SEK.

Ethical aspects: As low certainty of evidence did not show benefits of parenteral compared to oral clomipramine in patients with depression, and as infusion-related adverse events occurred, the benefit-risk balance could be negative. A negative benefit-risk balance for parenteral clomipramine may also apply to patients with OCD who have tried oral treatment without effect. Given the costs of the parenteral formulation, the principle of cost-effectiveness may not be met. The principle of autonomy is relevant for patients under compulsory care and severely ill patients – informed decisions may be a challenge in these patient groups.

Conclusion: In patients with depression, parenteral administration of clomipramine may not be favourable compared to oral administration. In patients with OCD, parenteral clomipramine may not be favourable when oral treatment has failed. For other critical and important outcomes and comparisons, evidence is either absent or does not allow for conclusions, but administration-related adverse reactions can occur with parenteral clomipramine. Given these findings and the high cost of the injectable formulation, ethical concerns may be raised, and further research including ECT or ketamine can be considered warranted.

2 Populärvetenskaplig sammanfattning på svenska

I tabellen nedan sammanfattas resultaten från en central jämförelse i denna HTA-rapport på ett övergripande sätt. Tabellen avser patienter med depression. Därefter följer en mer detaljerad redovisning av resultaten.

Vetenskapligt underlag för patienteffekter:	Fördel för klomipramin i infusionsform	Ingen/liten skillnad	Fördel för klomipramin i tablettform	Tilltro till resultatet	Studier saknas
Depressionssymptom inom två veckor (viktigaste måttet)		X		Låg	
Självmordsförsök					X
Död oavsett orsak					X
Depressionssymptom efter längre tid än två veckor		X		Låg	
Självmordstankar					X
Funktionsnivå					X
Avbruten behandling		X		Låg	
Vårdtid					X
Hälsorelaterad livkvalitet					X
Infusionsrelaterade biverkningar			X[1]	Mycket låg[4]	

	Klomipramin i infusionsform	Klomipramin i tablettform
Ekonomi		
Läkemedelskostnad i kronor[2]	3670-10189[3]	43

[1]Ytliga blodproppar och blodtrycksfall förekom i studierna för patienter som fått klomipramin i infusionsform.
[2]Första veckan, det vill säga den vecka som skiljer sig mellan jämförelsegrupperna. Inga andra kostnader än läkemedelskostnader ingår i beräkningen.
[3]Variationen i kostnad beror på behandlingsmodell.
[4]Samtliga studier som rapporterade resultat om infusionsrelaterade biverkningar använde en så kallad ”double-dummy-design”, vilket innebar att alla patienter fick infusioner som antingen innehöll klomipramin eller var overksamma (placebo).

Fråga: Är det bättre att få medicinen klomipramin via spruta direkt i blodet (infusion) för personer med svår depression eller tvångssyndrom, jämfört med att ta samma medicin som en tablett, eller jämfört med att få andra behandlingar som till exempel elbehandling, eller att ta sockerpiller (placebo), för att minska depressions- respektive tvångssymptom inom två veckor, och påverkas andra aspekter som är viktiga för patienten och sjukvården?

Bakgrund: Vid svåra fall av depression och tvångssyndrom ges ibland på sjukhuset klomipramin direkt i blodet, särskilt när andra behandlingar inte fungerat. Skäl som anges för att behandla på det sättet är att kroppen tar upp medicinen bättre och jämnare, att medicinen verkar snabbare, att man vet att patienten verkligen får i sig medicinen, och att det kan finnas en placeboeffekt förknippad med infusionsbehandling.

Metod: Med hjälp av etablerade metoder identifierades de vetenskapliga artiklar som kunde bidra till att besvara den aktuella frågan. De enskilda studierna kvalitetsgranskades, deras resultat summerades ihop, och tilltron till det sammanlagda resultatet bedömdes enligt vedertagna metoder.

Resultat: Rapporten baseras på 14 studier med totalt 418 patienter. Inga studier jämförde att ge klomipramin direkt i blodet med elbehandling eller läkemedlet ketamin, det vill säga de två jämförelser som vi på förhand definierat som särskilt relevanta. Inga

studier gav information om självmordsförsök, risken för död, självmordstankar, allmän funktionsförmåga, sjukhusvistelsens längd eller livskvalitet.

Vid ***depression*** visade en sammanvägning av fem studier med totalt 170 patienter att det är möjligt att klomipramin direkt i blodet inte är bättre än vanliga tabletter för att minska depressionssymptom inom två veckor, men en betydelsefull effekt kan inte helt uteslutas (låg tilltro till resultatet). När det gäller depressionssymtom på längre sikt, liksom risken för att behandlingen behöver avbrytas i förtid, tycks det inte heller finnas någon skillnad (låg tilltro till resultatet). Utifrån studierna gick det inte att dra slutsatser om biverkningar relaterade till att medicinen gavs direkt i blodet, men infusionsrelaterade biverkningar som till exempel ytliga blodproppar och blodtrycksfall redovisades i studierna och förekomsten överensstämde med det som står i FASS. Jämfört med andra behandlingar gick det inte att dra några slutsatser eller så fanns det inga studier. Jämfört med placebo är det möjligt att klomipramin direkt i blodet är bättre för att minska depressionssymptom inom två veckor (låg tilltro till resultaten).

Vid ***tvångssyndrom*** var underlaget för svagt för att kunna uttala sig om eventuella skillnader mellan klomipramin direkt i blodet eller i tablettform. Det fanns inga studier som jämförde klomipramin direkt i blodet med andra behandlingar. Jämfört med placebo visade en studie med 54 patienter att det är möjligt att klomipramin direkt i blodet inte är bättre för att minska tvångssymptom inom två veckor hos patienter som inte svarat på tablettbehandling med samma medicin, men en betydelsefull effekt kan inte uteslutas (låg tilltro till resultaten).

Kostnader: På grund av de stora osäkerheterna kring effekterna av att ge klomipramin direkt i blodet jämfört med andra behandlingsalternativ, samt avsaknaden av resultat för de viktiga jämförelserna med elbehandling och ketamin, redovisar vi här enbart läkemedelskostnaderna. Skillnaderna gäller endast den första veckan, eftersom alla patienter därefter får tablettbehandling i någon form. Beroende på vilken behandlingsregim som väljs, kostar klomipraminbehandling direkt i blodet antingen 3670 eller 10189 kronor. Behandling med tabletter kostar 43 kronor per vecka.

Etiska aspekter: Mot bakgrund av att nytta inte visats för att ge klomipramin direkt i blodet jämfört med i tablettform och att det finns risker förknippade med att ge behandling på detta sätt, kan nytta-risk-balansen för behandling vara negativ. Detsamma gäller jämförelsen med placebo för patienter med tvångssyndrom som provat medicinen i tablettform utan att få effekt. Med tanke på de högre kostnaderna för infusionsbehandling jämfört med vanliga tabletter, är det också möjligt att principen om kostnadseffektivitetet inte uppfylls; vår sammanställning av det vetenskapliga underlaget visar att den högre kostnaden inte kan motiveras genom bättre effekt. Autonomiprincipen, det vill säga rätten till självbestämmande, kan behöva tänkas på till exempel vid tvångsvård eller vid mycket svår sjukdom, då patienten inte alltid kan involveras vid beslut om behandling. Klomipramin ges dock i regel inte direkt i blodet till dessa patienter som tvångvårdsåtgärd.

Slutsats: För patienter med depression är det möjligt att klomipramin direkt via blodet inte är bättre än klomipramin som tas som tabletter. För patienter med tvångssyndrom som inte haft effekt av klomipramintabletter är det möjligt att klomipramin direkt via blodet inte är bättre än placebo. För andra viktiga resultat och jämförelser saknas studier eller så räcker de studier som finns inte till för att dra slutsatser. Infusionsrelaterade biverkningar kan dock inträffa när klomipramin ges direkt via blodet. Dessa fynd, tillsammans med att läkemedlet i infusionsform är mycket dyrare, väcker etiska frågor. Det behövs studier där elbehandling eller ketamin undersöks.

3 Summary of findings

Outcomes	Comparison	Studies without high RoB (number of patients)	Result	Certainty of evidence*
P1 = Patients with depression				
Depressive symptoms within 2 weeks	C1	5 RCTs (170 patients) *(whereof 3 were poolable)*	**No difference** Pooled change in HDRS scores, mean (SD): -1.27 (95% CI: -3.09; 0.54)	⊕⊕◯◯[1]
	C2	1 RCT (40 patients)	NA	⊕◯◯◯[2]
	C3	1 RCT (16 patients)	**Favours I** -6 (95% CI: -0.9; -11)	⊕⊕◯◯[3]
Suicide attempt	C1-C3	0	–	–
All-cause mortality	C1-C3	0	–	–
Depressive symptoms after more than two weeks	C1	4 RCT (143 patients) *(whereof 3 were poolable)*	**No difference** Pooled change in HDRS scores, mean (SD): -1.06 (95% CI: -4.70; 2.58)	⊕⊕◯◯[1]
	C2	2 RCT (83 patients)	NA	⊕◯◯◯[4]
	C3	0	–	–
Suicidal ideation	C1-C3	0	–	–
Global functioning	C1-C3	0	–	–
Treatment discontinuation	C1	3 RCT (112 patients) *(whereof 2 were poolable)*	**No difference** Peto OR: 1.05 (95% CI: 0.30; 3.71)	⊕⊕◯◯[1]
	C2	1 RCT (36 patients)	0 vs 0 events	⊕◯◯◯[5]
	C3	0	–	–
Length of hospital stay	C1-C3	0	–	–
HRQL	C1-C3	0	–	–
Adverse events related to administration via injection/infusion	C1	3 RCT (121 patients)	NA	⊕◯◯◯[2]
	C2	0	–	–
	C3	0	–	–

P2 = Patients with OCD				
OCD symptoms within 2 weeks	C1	2 RCT (47 patients)	NA	⊕◯◯◯[6]
	C2	0	–	–
	C3	1 RCT (54 patients)	**No difference** Change in Y-BOCS scores: -2.5 (95% CI: -5.6; 0.6)	⊕⊕◯◯[1]
Suicide attempt	C1-C3	0	–	–
All-cause mortality	C1-C3	0	–	–
OCD symptoms after more than two weeks	C1	1 RCT (15 patients)	NA	⊕◯◯◯[2]
	C2-C3	0	–	–
Suicidal ideation	C1-C3	0	–	–
Global functioning	C1-C3	0	–	–
Treatment discontinuation	C1	1 RCT (32 patients)	NA	⊕◯◯◯[2]
	C2-C3	0	–	–
Length of hospital stay	C1-C3	0	–	–
HRQL	C1-C3	0	–	–
Adverse events related to administration via injection/infusion	C1	1 RCT (32 patients)	NA	⊕◯◯◯[2]
	C2-C3	0	–	–

C = comparison, C1 = clomipramine non-parenterally, C2 = other treatment for the condition, C3 = placebo, CI = confidence interval, HDRS = Hamilton depression rating scale (higher scores denotes more severe symptoms; minimum clinically important difference: 2), HRQO = health-related quality of life, I = intervention, NA = not applicable (very low certainty of evidence), OCD = obsessive-compulsive disorder, P = patients, RCT = randomised controlled trial, RoB = risk of bias, Y-BOCS = Yale-Brown obsessive compulsive scale (higher scores denotes more severe symptoms; minimum clinically important difference: 4.9)

[1]Serious imprecision, some study limitations, some uncertainty regarding directness

[2]Very serious imprecision, some study limitations, some uncertainty regarding directness

[3]Serious indirectness, serious imprecision

[4]Serious study limitations, serious inconsistency, uncertain precision, some uncertainty regarding directness.

[5]Serious study limitations, very serious indirectness, very serious imprecision

[6]Very serious inconsistency, serious imprecision, some study limitations, some uncertainty regarding directness

*High certainty ⊕⊕⊕⊕: We are very confident that the actual effect lies close to that of the estimate of the impact.

Moderate certainty ⊕⊕⊕◯: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different to the estimate of the effect.

Low certainty ⊕⊕◯◯: Confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low certainty ⊕◯◯◯: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

4 Abbreviations

CANMAT = Canadian Network for Mood and Anxiety Treatments
CBT = cognitive-behavioural therapy
ECT = electroconvulsive therapy
RDP = Exposure and Response Prevention
HDRS = Hamilton depression rating scale
HRQL = health-related quality of life
ICBT = Internet-delivered cognitive behaviour therapy
IPT = interpersonal psychotherapy
MADRS = Montgomery Åsberg Depression Rating Scale
OCD = obsessive-compulsive disorder
RCT = randomised controlled trial
SNRI = serotonin-norepinephrine reuptake inhibitor
SSRI = selective serotonin reuptake inhibitor
TCA = tricyclic antidepressant
Y-BOCS = Yale-Brown obsessive compulsive scale

5 Background

Diseases/disorders of interest and their degree of severity

Depression
Depression, including both the unipolar and bipolar types, is characterised by persistent feelings of sadness, hopelessness, and loss of interest in activities, significantly impacting daily functioning and overall well-being (American Psychiatric Association, 2013). The severity of the condition is high or very high. The condition has been associated with an increased risk of premature death, with individuals reportedly having a two- to three-fold higher risk compared to the general population (Zhang et al., 2023; Meng et al., 2020). Depression has also been reported to contribute to cognitive impairment and cardiovascular disease as well as a significantly reduced quality of life (Meng et al., 2020; Yin et al., 2024).

Obsessive-compulsive disorder
Obsessive-compulsive disorder (OCD) is a persistent mental disorder that manifests through unwanted, intrusive thoughts, i.e., obsessions, that lead to repetitive behaviours or mental rituals alleviating anxiety and distress, i.e., compulsions (American Psychiatric Association, 2013, World Health Organization, 1992). OCD interferes with work performance, personal relationships, and everyday activities, and the degree of severity can be considered high or moderate. The condition often results in long-term challenges for those affected (Garnaat et al., 2015). Without appropriate treatment, OCD typically becomes a lifelong condition, potentially causing permanent impairment (Bloch et al., 2013). Further, OCD has been associated with an increased risk of premature death (Meier et al., 2016).

Prevalence and incidence

Depression
The point prevalence of unipolar depression in Sweden has been estimated at 5.2% (Johansson et al., 2013). The lifetime prevalence of unipolar depression is reportedly 35% for women and 25% for men (Johansson et al., 2013; Pasma et al., 2023). The annual incidence of depression in Sweden has been estimated at 4.3–7.6 per 1,000 person-years, which translates to 0.4–0.8% of the adult population (Lejtzén et al., 2014).

Obsessive-compulsive disorder
Worldwide, the lifetime prevalence of OCD is estimated at 1.3%, with women 1.6 times more likely to experience OCD compared to men (Fawcett et al., 2020). The disorder typically emerges in late adolescence or early adulthood, with a mean onset age of 19–20 years (Brakoulias et al., 2017).

Present treatment

Depression
The treatment of depression involves a multifaceted approach combining pharmacological interventions, psychotherapy, and in some cases, electroconvulsive therapy (ECT). For unipolar depression, the primary pharmacological treatments include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and atypical antidepressants (e.g., bupropion and mirtazapine). The duration of treatment varies but often lasts several months to a year or more for maintenance therapy.

For bipolar depression, the treatment approach is more complex due to the risk of inducing manic episodes (Shire et al., 2025). Common pharmacological interventions for bipolar depression include mood stabilizers (e.g., lithium, valproic acid), second-generation antipsychotics, and antidepressants in combination with mood stabilizers. Psychotherapy, particularly cognitive-behavioural therapy (CBT), is often used in conjunction with medication but to a lesser extent compared with unipolar depression. For both unipolar and bipolar depression, tricyclic antidepressants (TCAs), like clomipramine, can be considered (Anderson, 2020; Steffens, 1997). However, they are not first-line options due to their safety profile including anticholinergic effects and a risk of life-threatening overdose, and the availability of newer antidepressant treatments (Kamp et al., 2024; Santandreu et al., 2024; Machado et al., 2006).

Inpatient care may be necessary for patients with depression, particularly when treatment resistance, active suicidality, and severe psychotic or mixed symptoms occur. While the goal is rapid and effective alleviation of depressive symptoms, there is no clear-cut first-line treatment in this care context. ECT may be an alternative, especially for patients with difficult-to-treat depressive states (Schoeyen, 2015; Pagnin et al., 2004). However, ECT is resource-demanding, not consistently effective or accepted, and implies a risk of cognitive side effects, especially in young patients (Loef et al., 2024; Kronsell et al., 2019).

Obsessive-compulsive disorder
CBT and SSRIs are the current first-line treatments for OCD (Läkemedelsverket, 2016; Skapinakis et al.,2016). The duration of treatment varies but often lasts several months to years. Internet-delivered cognitive behavior therapy (ICBT) for OCD has been implemented in the regular healthcare system in Sweden since 2018, making such treatment more accessible (Vigerland et al., 2024). For severe, treatment-resistant cases, intensive residential treatment programs may be utilised. Clomipramine and other TCAs, while less commonly used than SSRIs, constitute a treatment option, particularly in treatment-resistant cases (de Oliveira et al., 2023; Skapinakis et al., 2006). As in depression, the use of TCAs is limited by their safety profile.

The normal pathway through the healthcare system and current wait time for medical assessment/treatment

Depression
In Sweden, about 70% of the patients with unipolar depression are diagnosed and treated in primary care (Asp, 2022; Socialstyrelsen, 2010). Those presenting with therapy-refractory depression, a high risk of suicide, or comorbid psychiatric conditions are typically referred to psychiatric specialists for more intensive care. The initial evaluation by a psychiatric specialist usually occurs within three months of referral. Patients may also self-refer to tertiary care. In cases of acute symptoms, severe functional impairment, or imminent risk of suicide, immediate hospital admission may be warranted. Compulsory care is sometimes required, especially for patients exhibiting psychotic features associated with depression.

For patients with bipolar disorder, initial screening often occurs in primary care, followed by further psychiatric assessments as needed. Outpatient follow-up usually occurs in specialist psychiatric clinics. Inpatient admissions may be required to manage manic, depressive, or mixed episodes. Bipolar patients often need regular healthcare contact due to the chronic nature of the condition, which necessitates ongoing management to prevent relapse.

Wait times for mental health services in Sweden have been a concern. The target for initial assessment is within 90 days, but actual wait times can vary significantly depending on location and service demand. In some areas, patients may wait several months for psychotherapy or specialised psychiatric care. Patients requiring inpatient psychiatric care are typically admitted through two main pathways: the emergency psychiatric department or direct referral from outpatient clinics. Admission to an acute psychiatric unit is typically warranted for patients with treatment-resistant conditions, high suicide risk, and severe symptoms like severe psychotic, catatonic, or neurovegetative symptoms.

Obsessive-compulsive disorder
Typically, OCD patients' pathway through the Swedish healthcare system begins with an initial assessment in primary care or through specialised OCD teams. Outpatient follow-up typically involves both primary care and specialised psychiatric clinics, depending on the severity of the condition and the patient's needs. In Region Västra Götaland, there are specialised OCD teams that provide treatment for moderate to severe cases. For severe cases, or when outpatient treatment is ineffective, inpatient treatment may be considered. This is typically reserved for patients with very severe symptoms, those at risk of self-harm, or those who have not responded to outpatient interventions. Current wait times for assessment and treatment initiation can vary but may be several months in some cases.

Number of patients per year who undergo current treatment regimen

Depression
In 2023, the total number of patients with depression per 100,000 inhabitants who received inpatient care in Sweden was 104.2 for all age groups and both genders (Socialstyrelsen, 2019). This total represents the combined rate of patients with depression who received inpatient care across all the listed mood disorders (F31 Bipolar disorder, F32 Depressive episode, F33 Recurrent depressive disorder, and F34 Persistent mood disorders). However, it is important to note that not all individuals with depression require inpatient care, and many may not seek or receive any treatment at all. It has been suggested that approximately 47% of those with depression and/or anxiety in Sweden seek treatment (Wallerblad et al., 2012)

Obsessive-compulsive disorder
In 2023, the number of patients with OCD receiving inpatient care in Sweden was 3.3 per 100,000 inhabitants. This figure applies to the diagnostic code F42 (OCD) and covers all age groups (0–85+) and both genders. There is no publicly available figure for the total number of patients seeking care in Region Västra Götaland. The regional specialist clinic for moderate to severe OCD received 257 referrals in 2024, reflecting just a fraction of those affected.

Present recommendations from medical societies or health authorities

Depression
The Swedish National Board of Health and Welfare recommends CBT or Interpersonal Psychotherapy (IPT) as first-line treatments for mild to moderate depression (Socialstyrelsen, 2021). For moderate to severe depression, antidepressant medications, particularly SSRIs, are often recommended, often in combination with psychotherapy. Regular follow-up and monitoring of treatment response are emphasized, and ECT is considered for severe, treatment-resistant depression. These recommendations generally align with international guidelines, such as the clinical guidelines of the Canadian Network for Mood and Anxiety Treatments (CANMAT) (Lam et al., 2024) and the National

Institute for Health and Care Excellence (NICE) in the United Kingdom (2022). To our knowledge, there are no specific international or national guidelines for the inpatient treatment of depressive states. According to the guidelines from the Swedish National Board of Health and Welfare (Socialstyrelsen, 2021), infusion with a TCA, including clomipramine, can be considered in adults with severe depression in exceptional cases; however, it is given a low priority (priority 9).

Obsessive-compulsive disorder

The Swedish National Board of Health and Welfare recommends CBT with Exposure and Response Prevention (ERP) as first-line treatment for OCD in both adults and children. SSRIs are recommended as an alternative or adjunct to CBT. For treatment-resistant cases, augmentation with antipsychotics or switching to clomipramine is suggested (Läkemedelsverket, 2016). Parenteral administration is not mentioned in these recommendations. NICE guidelines for OCD also prioritise CBT and SSRIs as first-line treatments for OCD (NICE 2005). According to the NICE guidelines, clomipramine should be considered for adults with OCD after an adequate trial of at least one SSRI and found ineffective or poorly tolerated, or if the patient prefers clomipramine or has had a previous good response to it. The NICE guidelines do not mention or prioritise parenteral administration of clomipramine. The CANMAT guidelines for OCD recommend SSRIs (escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) as first-line treatments when medication is required. Second-line options include citalopram, clomipramine, mirtazapine, and venlafaxine XR. Third-line treatments (for resistant cases) include IV citalopram/clomipramine, duloxetine, phenelzine, tramadol, and tranylcypromine (Katzman et al., 2014).

6 Health Technology at issue: Parenteral Clomipramine

Parenteral clomipramine, also known as Anafranil® infusions, is utilised as a treatment option for severe cases of depression and OCD, especially in treatment-resistant conditions and inpatient care. This method of administration is typically conducted in an inpatient or hospital setting due to the need for close monitoring of vital signs and cardiovascular adverse reactions.

Treatment regimens
The two most common treatment regimens are pulse loading and gradual titration. Pulse loading involves parenteral (commonly intravenous) administration of high doses of clomipramine over a short period, typically 1–2 days, with a standard regimen being 150 mg on day 1 and 200 mg on day 2. Conversely, gradual titration implies starting with a low dose, often 50 mg/day, and gradually increasing the dose over several days, for instance, to a maximum of 225 mg/day over 5–7 days. The duration of treatment of intravenous administration can vary from 2 to 14 days, depending on the specific protocol and patient response.

Post-treatment strategies
After the initial intravenous administration of clomipramine, patients are often transitioned to oral treatment. Based on the patient's response and the clinician's decision, patients may be switched to oral clomipramine, usually starting at 75 mg/day and potentially increasing to 150-250 mg/day, or another antidepressant.

Rationale for the treatment
The main arguments for using clomipramine infusion are the following:

1. ***Bioavailability:*** Parenteral administration bypasses the gastrointestinal tract and first-pass hepatic metabolism, which results in more predictable bioavailability compared to oral administration (Balant-Gorgia et al.,1991). The bioavailability of oral clomipramine is approximately 50% due to first-pass metabolism to the active metabolite desmethylclomipramine (Summary of Product Characteristics, Anafranil®).
2. ***Metabolite profile****:* Parenteral clomipramine results in a higher ratio of the parent drug to its metabolites, particularly desmethylclomipramine (Evans et al., 1980). This may be significant because clomipramine is a potent serotonin reuptake inhibitor, while its metabolites primarily inhibit noradrenaline reuptake (Gillman, 2007). Thus, the higher ratio of clomipramine to its metabolites in plasma following parenteral administration may result in more potent serotonin reuptake inhibition.
3. ***Steady-state achievement:*** Parenteral administration allows for quicker attainment of steady-state plasma concentrations than oral administration, potentially leading to faster onset of therapeutic effect.
4. ***Compliance:*** Parenteral administration implies that patients receive the full prescribed dose, eliminating concerns about missed doses or inconsistent oral intake. Furthermore, the clinical setting for parenteral treatment allows for close monitoring and supportive care, potentially enhancing patient engagement and adherence to the treatment plan.
5. ***Placebo effect:*** Studies have shown injectable placebos elicit a more pronounced placebo response than oral placebos (Jones et al., 2021).

6. ***Potential underutilisation of TCAs:*** This argument refers to the broader context of medical praxis where older medications, such as TCAs, can sometimes be overlooked despite potential benefits (Anderson, 2000; Greenslit et al., 2012).

7 Focused question

In patients with depression or OCD, is parenteral administration of clomipramine superior to oral clomipramine, other treatments, or placebo in terms of reducing depressive symptoms and obsessive-compulsive symptoms within two weeks, as well as other important outcome measures?

Patients (P)
P1: Patients with depression diagnosed in healthcare (unipolar and bipolar)
P2: Patients with OCD

Intervention (I)
I: Clomipramine via parenteral administration

Comparison (C)
C1: Clomipramine via other routes of administration (not parenterally)
C2: Other treatment (e.g. electroconvulsive therapy or other medication(s))
C3: Placebo

Outcomes (O)
Critical for decision-making

- Depressive symptoms (P1) or OCD symptoms (P2) within two weeks
- Suicide attempt
- All-cause mortality

Important for decision-making

- Long-term depressive symptoms (P1) or OCD symptoms (P2) (>2 weeks)
- Suicidal ideation
- Global functioning
- Treatment discontinuation
- Length of hospital stay
- Health-related quality of life (HROL)
- Adverse events related to administration via injection/infusion (e.g. thrombophlebitis, infection, anaphylaxis)

Restricted to:
Randomised controlled trials (RCT)
Studies written in English, Swedish, Danish or Norwegian

Predefined subgroup analyses
P: older patients (⩾65 years); severe depression with melancholic or psychotic symptoms
I: Monotherapy; add-on therapy
C2: ECT; ketamine

The patient organisations "Balans" (depression) and "Ananke" (OCD) were asked to review the outcomes, and global functioning added thanks to the former.

8 Method

The systematic review was registered with PROSPERO (CRD420250654029).

Systematic literature search (Appendix 1)

Two information specialists (J.G., T.S.) performed systematic searches in Medline, Embase, the Cochrane Library and PsycInfo (30 September 2024). Websites of Scandinavian national and regional HTA organisations were visited in April 2025. A citation search (both backward and forward) of all included articles, as well as a selection of excluded systematic reviews, was done in Web of Science Core Collection. Search strategies, eligibility criteria, and a graphic presentation of the selection process are presented in Appendix 1. The two authors who conducted the literature searches independently screened the retrieved abstracts to determine their eligibility for full-text retrieval, i.e. those not clearly outside the scope of this HTA. The screening process was conducted using the Rayyan tool (Ouzzani et al., 2016). Any disagreements were resolved through consensus. All retrieved full-text reports were independently read by at least two authors. In a consensus meeting, we made the final decision on which reports to include in the current HTA, i.e. those that fulfilled the PICO criteria. For articles excluded in consensus, after full-text reading, reasons for exclusion are presented in Appendix 3.

Critical appraisal and certainty of evidence

For included studies, data on design were extracted, as well as data regarding participant characteristics, the intervention and the control groups including treatment regimen, and outcomes reported (Appendix 2). Measures of effect and number of events were also extracted. For the outcome regarding depressive and OCD symptoms within two weeks, we chose to extract the results that were closest to one week and closest to two weeks, and to pool the latter if data were available, otherwise the former. For the outcome regarding depressive and OCD symptoms after more than two weeks, we chose to extract the results that were closest to four weeks and to pool if possible. All data were independently extracted by at least two authors, with discrepancies resolved in consensus.

The included articles were independently appraised by at least two authors using the Cochrane Risk of Bias tool for randomised trials (RoB 2.0), followed by consensus discussions. A checklist developed by HTA-centrum, Sahlgrenska University Hospital, was used to assess the domains directness and precision. The assessments are summarised in Appendix 5.

If two or more studies provided poolable data regarding the outcomes at issue, random effects meta-analyses were performed to obtain weighted mean differences, including 95% confidence intervals (CI), using Review Manager 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Peto odds ratio was used in case of zero-event arms as this method does not require corrections (Cochrane Handbook for Systematic Reviews of Interventions, Chapter 10). Meta-analyses based on studies without major risk of bias were beforehand determined to be the primary basis for the conclusions. Beforehand, we also determined that changes in the Hamilton depression rating scale (HDRS; P1) scores and Yale-Brown obsessive compulsive scale (Y-BOCS) scores would be the primary basis for conclusions.

The certainty of evidence was assessed according to GRADE (Atkins et al., 2004), with reasons for downgrading described. Summary results per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (pages 10–11).

Ongoing research

A search in Clinicaltrials.gov (4 March 2025) using the search terms (chlorimipramine OR chlomipramine OR anafranil OR hydiphen OR clomipramine) identified 37 trials.

9 Results

Search results and study selection (Appendix 1)

The literature and citation search identified 4,973 records after removal of duplicates. After reading the abstracts, 4,684 records were excluded, and 289 reports were sought for retrieval. Six reports could not be retrieved, and 14 reports were finally included in the HTA (Appendix 2).

Included studies

The PICO of this HTA was fulfilled in 14 RCTs (P1: n=11; P2: n=3) including a total of 418 patients (P1: n=317; P2: n=101) (Appendix 2). The studies were performed in the United States (n=6), Italy (n=3), France (n=2), Belgium (n=1), Germany (n=1), and the United Kingdom (n=1). Ten RCTs were double-blind, two were single-blind, and two were open label.

The intervention was intravenous clomipramine with gradual titration in eight RCTs, with pulse loading in four RCTs, and with a fixed dose in two RCTs. The comparison was oral clomipramine (C1) in eight RCTs, another medication (C2) in four RCTs, and placebo (C3) in two RCTs. ECT and ketamine was not used as comparison in any RCT. Ten RCTs were assessed not have a high risk of bias (Appendix 5).

Results per outcome för patients with depression (P1)

Outcomes critical for decision-making

Depressive symptoms within two weeks (appendix 4.1)

Regarding the HDRS scale, the predetermined primary scale for conclusions, a variety of abbreviations and item selections were used in the RCTs, reflecting the development of this scale over the years. In this evidence synthesis, we considered these data poolable if a summarised result including the items at issue were reported. Higher HDRS scores indicate greater severity, and an HDRS total score ≥23 indicates severe depression.

Regarding the ***comparison with oral clomipramine (C1)***, six RCTs provided data, whereof five double-blind RCTs, including a total of 170 patients, were assessed not to have a high risk of bias. Two of these could not be pooled; one did not report a summarised HDRS result (Escobar et al., 1973), and the other used the Montgomery Åsberg Depression Rating Scale (MADRS) (Spreux-Varoquaux et al., 1996). A meta-analysis of the changes in HDRS scores at two weeks for the remaining RCTs is presented in Figure 1. At one week, a meta-analysis of these studies revealed a mean difference of -0.71 (95% CI: -3.20; 1.77; I2=62%). In the RCT reporting results using MADRS, the difference in change was -2.9 (95% CI: -13.3; 7.5).

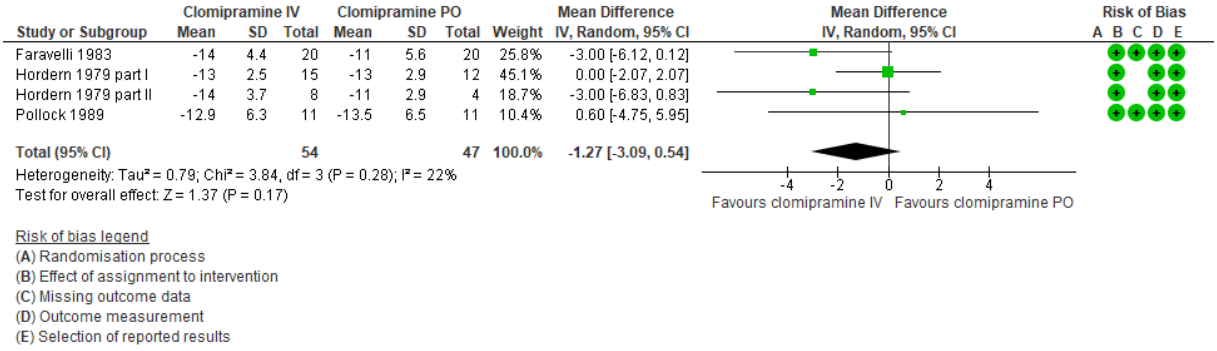


Figure 1 Forest plot and meta-analysis of changes in HDRS scores at two weeks for the comparison intravenous versus oral clomipramine (unfilled risk of bias space denotes some concerns regarding risk of bias).

In the GRADE process, we downgraded one step because of serious imprecision; the non-significant pooled result had a wide CI including the minimum clinically important difference of two HDRS points (Hengartner et al., 2022). The same applied to the RCT using MADRS, where the non-significant result had a wide CI including the minimum clinically important difference of three MADRS points (Hengartner et al., 2022). We also downgraded one step because of some study limitations and some uncertainty regarding directness.

> ***Conclusion:*** In patients with depression, intravenous clomipramine may not be superior to oral administration in terms of reducing depressive symptoms within two weeks, but a clinically relevant effect cannot be excluded (low certainty of evidence, ⊕⊕◯◯).

Regarding the ***comparison with other treatments (C2)***, three RCTs contributed results. The comparison was either maprotiline, citalopram, or salbutamol, all administered intravenously. One of them, comparing intravenous clomipramine with intravenous maprotiline and including a total of 40 patients, was assessed not to have a high risk of bias (Drago et al., 1983) and the results were described as "no significant differences in the two groups".

In the GRADE process, we downgraded two steps because of very serious imprecision as the standard deviations in the randomisation groups were large. We also downgraded one step because of some study limitations and some uncertainty regarding directness.

> ***Conclusion:*** In patients with depression, it is uncertain whether there is any difference using intravenous clomipramine compared to intravenous maprotiline in terms of reducing depressive symptoms within two weeks (very low certainty of evidence, ⊕◯◯◯).

Regarding the ***comparison with placebo (C3)***, one RCT, including 16 adolescents and without a high risk of bias, contributed results (Sallee et al., 1997). The reduction in HDRS scores at day 6 was larger in the intervention group, mean difference: -6.0 (95% CI: -0.9; -11).

In the GRADE process, we downgraded one step because of serious indirectness, for instance as the study population was restricted to adolescents with an initial 4-week washout for antidepressant. We also downgraded one step because of serious imprecision as the 95% CI was wide.

Conclusion: In patients with depression, intravenous clomipramine may be superior to placebo in terms of reducing depressive symptoms within two weeks (low certainty of evidence, ⊕⊕◯◯).

Suicide attempts and all-cause mortality

No studies reported results for the critical outcomes suicide attempt and all-cause mortality.

Outcomes important for decision-making

Depressive symptoms after more than two weeks (appendix 4.2)

Regarding the ***comparison with oral clomipramine (C1)***, five RCTs contributed data, whereof four double-blind RCTs including a total of 143 patients were assessed not to have a high risk of bias. One of these did not report a summarised HDRS result (Escobar et al., 1973). A meta-analysis of the changes in HDRS scores for the remaining RCTs is presented in Figure 2.

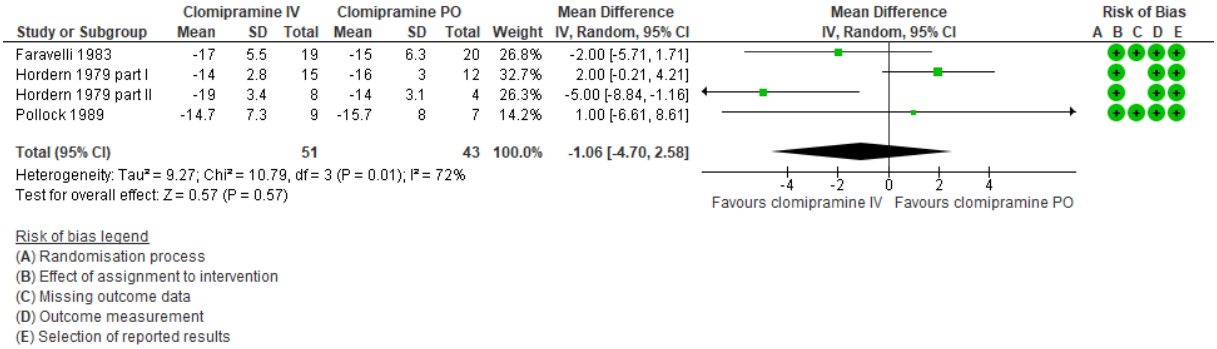


Figure 2 Forest plot and meta-analysis of changes in HDRS scores at four weeks for the comparison intravenous versus oral clomipramine (unfilled risk of bias space denotes some concerns regarding risk of bias)

In the GRADE process, we downgraded one step because of serious imprecision as the non-significant pooled result had a wide CI including the minimum clinically important difference of two HDRS points (Hengartner et al., 2022). We also downgraded one step because of some study limitations, some inconsistency, and some uncertainty regarding directness. The inconsistency introduced by the results of the second part of the RCT by Hordern et al. (1979) was not considered to merit downgrading as these results were based on outpatients with initial HDRS scores below 23, i.e. conditions that do not correspond to severe depression.

Conclusion: In patients with depression, intravenous clomipramine may not be superior to oral administration in terms of reducing depressive symptoms at four weeks (low certainty of evidence, ⊕⊕◯◯).

Regarding the ***comparison with other treatments (C2)***, two RCTs contributed results, either against maprotiline or salbutamol, all administered intravenously. They included a total of 83 patients, and both were assessed to have a high risk of bias. The mean difference (7.6 (95% CI: 5.6; 9.6) favoured intravenous salbutamol in one RCT, but these results were not reflected in the response rate (Lecrubier et al., 1980). The other RCT had similar response rates in both randomisation groups (Fähndrich et al., 1983).

In the GRADE process, we downgraded one step because of serious study limitations and one step because of serious inconsistency. We also downgraded one step because of uncertain precision and some uncertainty regarding directness.

Conclusion: In patients with depression, it is uncertain whether there is any difference using intravenous clomipramine compared to other intravenous medications in terms of reducing depressive symptoms within two weeks (very low certainty of evidence, ⊕◯◯◯).

Regarding the ***comparison with placebo (C3)***, no RCT contributed data

Treatment discontinuation (appendix 4.3)

Regarding the ***comparison with oral clomipramine (C1)***, three double-blind RCTs including a total of 112 patients contributed data. They were all assessed not to have a high risk of bias. One RCT did not clearly report randomisation group allocation for one treatment discontinuation (Pollock et al., 1989) and could therefore not be pooled. A meta-analysis including the two RCTs providing poolable data is presented in Figure 2.

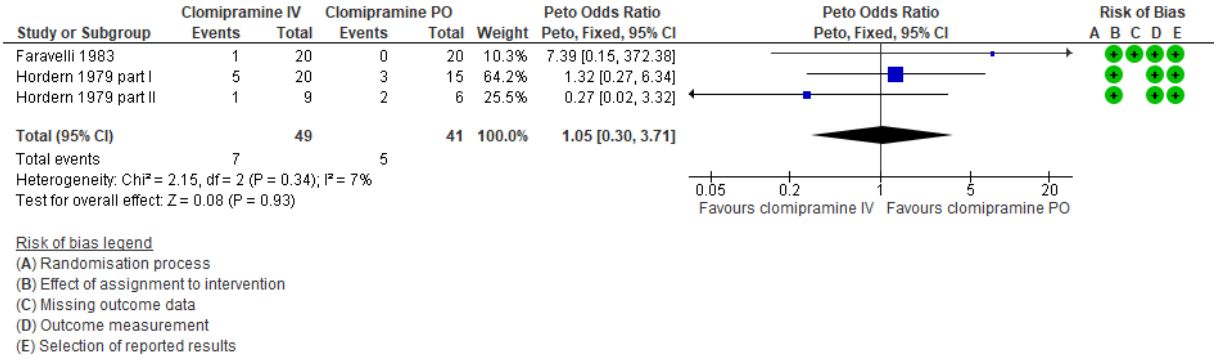


Figure 2 Forest plot and meta-analysis of treatment discontinuation for the comparison intravenous versus oral clomipramine (unfilled risk of bias space denotes some concerns regarding risk of bias)

In the GRADE process, we downgraded one step because of serious imprecision; the non-significant pooled result had a wide CI. We also downgraded one step because of some study limitations and some uncertainty regarding directness.

Conclusion: In patients with depression, there may be no difference in treatment discontinuation rates for intravenous compared with oral clomipramine (low certainty of evidence, ⊕⊕◯◯).

Regarding the ***comparison with other treatments (C2)***, one RCT, using intravenous citalopram as comparison and with a high risk of bias, contributed the information that none of the 36 participants discontinued (Altamura et al., 2008).

In the GRADE process, we downgraded one step because of serious study limitations. In addition, we downgraded because of very serious indirectness as, for instance, the patients were restricted to outpatients and low doses were used. We also downgraded because of very serious imprecision as no events occurred.

Conclusion: In patients with depression, it is uncertain whether treatment discontinuation rates differ between intravenous clomipramine and intravenous citalopram (very low certainty of evidence, ⊕◯◯◯).

Regarding the ***comparison with placebo (C3)***, no RCT contributed data

Adverse events related to administration via injection/infusion (appendix 4.4)

Regarding the ***comparison with oral clomipramine (C1)***, three double-blind RCTs including a total of 121 patients contributed data. They were all overall assessed not to

have a high risk of bias. As all RCTs had a double-dummy design, procedure-related adverse events could occur in both randomisation groups; 1 versus 1 event of thrombophlebitis occurred in these RCTs. In all, 5 versus 2 events related to the cardiovascular system occurred in the randomisation groups, whereof 4 versus 2 with hypotension. A forest plot of all adverse events related to administration via injection/infusion is presented in Figure 3. No meta-analysis was performed because of clinical heterogeneity of adverse events.

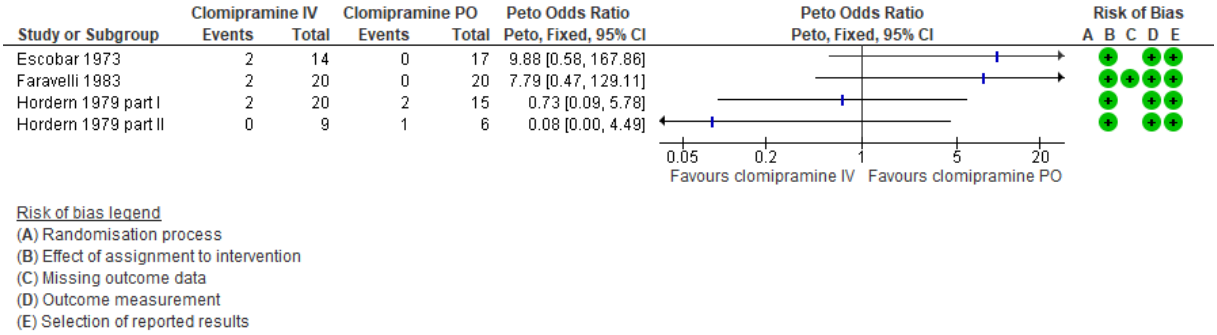


Figure 3 Forest plot of adverse events related to administration via injection/infusion for intravenous versus oral administration of clomipramine (unfilled risk of bias space denotes some concerns regarding risk of bias)

In the GRADE process, we downgraded two steps because of very serious imprecision as the CIs were large. We also downgraded one step because of some study limitations and some uncertainty regarding directness.

> ***Conclusion:*** Based on very low certainty of evidence (⊕◯◯◯), infusion-related adverse event rates in patients with depression are in line with the SPC.

Regarding the ***comparison with other treatments (C2)*** as well as the ***comparison with placebo (C3)***, no RCT contributed data

Suicidal ideation, global functioning, length of hospital stay and HRQL
No studies reported results for the important outcomes Suicidal ideation, global functioning, length of hospital stay and HRQL.

Results per outcome för patients with OCD (P2)

Outcomes critical for decision-making

OCD symptoms within two weeks (appendix 4.1)
Regarding the ***comparison with oral clomipramine (C1)***, two double-blind RCTs including a total of 47 patients contributed data. They were both assessed not to have a high risk of bias. One of these included patients that had previously not responded to serotonin reuptake inhibitors including clomipramine (Koran et al., 2006). A forest plot of changes in Y-BOCS scores at one week is presented in Figure 4. e to clinical heterogeneity, we refrained from performing a meta-analysis.

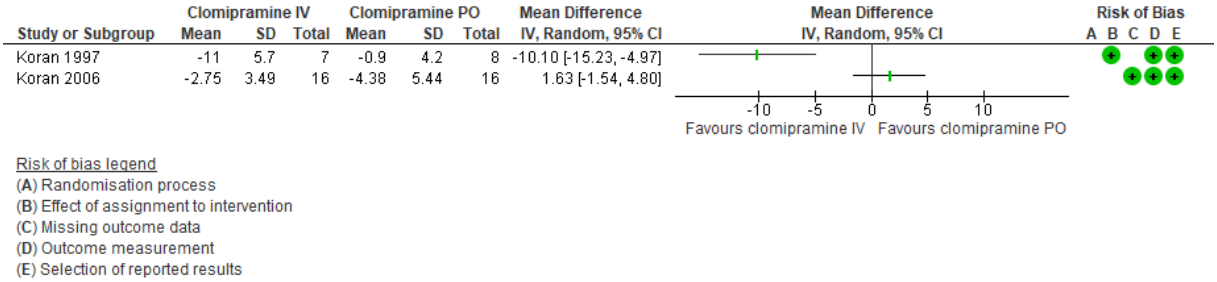


Figure 4 Forest plot of changes in Y-BOCS scores at one week for the comparison intravenous versus oral clomipramine (unfilled risk of bias space denotes some concerns regarding risk of bias)

In the GRADE process, we downgraded two steps because of very serious inconsistency; the result of the two RCTs diverged considerably. We also downgraded one step because of serious imprecision as the studies were small with wide CIs. There were also some study limitations and some uncertainty regarding directness, but further downgrading was not possible.

> ***Conclusion:*** In patients with OCD, it is uncertain whether intravenous clomipramine differs from oral clomipramine regarding effects on OCD symptoms at one week (very low certainty of evidence, ⊕◯◯◯).

Regarding the ***comparison with other treatments (C2)***, no RCT contributed data

Regarding the ***comparison with placebo (C3)***, one RCT, including 54 patients and without a high risk of bias, contributed data (Fallon et al., 1998). The patients were treatment refractory to oral clomipramine. There was no significant difference in Y-BOCS scores among those who completed the entire treatment (14 infusions): mean difference: -2.5 (95% CI: -5.6; 0.6).

In the GRADE process, we downgraded one step because of serious imprecision; the non-significant result had a wide CI including the minimum clinically important difference of 4.9 Y-BOCS points (Cohen et al., 2024). We also downgraded one step because of some study limitations and some uncertainty regarding directness.

> ***Conclusion:*** In patients with OCD refractory to oral clomipramine, intravenous clomipramine may not be superior to placebo regarding effects on OCD symptoms at two weeks, but a clinically relevant effect cannot be excluded (low certainty of evidence, ⊕⊕◯◯).

Suicide attempts and all-cause mortality

No studies reported results for the critical outcomes suicide attempt and all-cause mortality.

Outcomes important for decision-making

OCD symptoms after more than two weeks (appendix 4.2)

Regarding the ***comparison with oral clomipramine (C1)***, one double-blind RCT, including 15 patients and without a high risk of bias, contributed data for 13 patients at three weeks, with a non-significant change in Y-BOCS scores: -4.5 (95% CI: -16.5; 7.5) (Koran et al., 1997).

In the GRADE process, we downgraded two steps because of very serious imprecision; the CI was very large. We also downgraded one step because of some study limitations and some uncertainty regarding directness.

> ***Conclusion:*** In patients with OCD, it is uncertain whether treatment discontinuation rates differ between intravenous and oral clomipramine (very low certainty of evidence, ⊕◯◯◯).

Regarding the ***comparison with other treatments (C2)*** as well as the ***comparison with placebo (C3)***, no RCT contributed data

Treatment discontinuation (appendix 4.3)

Regarding the ***comparison with oral clomipramine (C1)***, one double-blind RCT, including 32 patients and without a high risk of bias, contributed data (Koran et al., 2006). Three versus five patients discontinued treatment (out of 16 in each randomisation group).

In the GRADE process, we downgraded two steps because of very serious imprecision due to few patients and few events. We also downgraded one step because of some study limitations and some uncertainty regarding directness.

> ***Conclusion:*** In patients with OCD, it is uncertain whether treatment discontinuation rates differ between intravenous and oral clomipramine (very low certainty of evidence, ⊕◯◯◯).

Regarding the ***comparison with other treatments (C2)*** as well as the ***comparison with placebo (C3)***, no RCT contributed data

Adverse events related to administration via injection/infusion (appendix 4.4)

Regarding the ***comparison with oral clomipramine (C1)***, one double-blind RCT, including 32 patients and without a high risk of bias, contributed data (Koran et al., 2006). Two patients in each randomisation group experienced adverse events related to the infusion, all events related to the cardiovascular system.

In the GRADE process, we downgraded two steps because of very serious imprecision due to few patients and few events. We also downgraded one step because of some study limitations and some uncertainty regarding directness.

> ***Conclusion:*** Based on very low certainty of evidence (⊕◯◯◯), infusion-related adverse event rates in patients with OCD are in line with the SPC.

Regarding the ***comparison with other treatments (C2)*** as well as the ***comparison with placebo (C3)***, no RCT contributed data

Suicidal ideation, global functioning, length of hospital stay and HRQL

No studies reported results for the important outcomes Suicidal ideation, global functioning, length of hospital stay and HRQL.

10 Organisational aspects

Time frame for the putative introduction of the new health technology

The present HTA does not concern the introduction of a new health technology; parenteral administration of clomipramine has been utilised since the 1970s in various centers worldwide.

Present use of the technology in other hospitals in Region Västra Götaland

As a basis for this HTA, a national survey was conducted during the first quarter of 2025 regarding the use of parenteral clomipramine in Swedish psychiatric clinics. It was carried out through a six-question online survey targeting clinical managers at clinics with inpatient psychiatric units (Appendix 6).

In total, 37 unique clinics from all 21 regions responded. Of these, 31 (84%) reported using parenteral clomipramine as a treatment method over the past three years. Parenteral clomipramine had been utilised in all regions except for Region Stockholm (four responding clinics) and Region Kalmar (two responding clinics). Parenteral clomipramine was considered an alternative to ECT in certain cases by 29 clinics (78%). The primary indications for treatment were reported to be major depressive disorder, OCD, and anxiety disorder. In 14 (38%) clinics, parenteral clomipramine was used 1–2 times per year. In contrast, three clinics (Sahlgrenska University Hospital, NU Hospital Group (NÄL Hospital Trollhättan and Uddevalla Hospital), and Östersund Hospital) used it more than 12 times per year. These results, although not adjusted for the number of admissions, suggest that usage may be more common in Region Västra Götaland.

Based on medical records from Sahlgrenska University Hospital, 9,934 psychiatric admissions for depressive conditions were identified between 2016 and 2022). After applying the following inclusion criteria: hospital stay >6 days and age 18–65 years, and excluding non-affective psychosis, bipolar disorder, dementia, brain injury, and withdrawal syndrome, 4,903 admissions were included in an analysis. Parenteral clomipramine was used during 199 admissions (4.1%, 95% CI: 3.5; 4.7), and in 41 (20.6%) of these, such treatment was combined with ECT. Twenty-five patients received clomipramine during multiple admissions. ECT was given during 599 admissions (12.2%, 95% CI: 11.3;13.2), and during 558 (93.2%) of these admissions, no parenteral clomipramine was administered.

Consequences of the health technology for personnel

Parenteral clomipramine administration requires dedicated nursing resources for monitoring of vital signs, including blood pressure and pulse, before treatment and every 15 minutes during the infusion, and extended documentation. Therefore, the affected personnel group is primarily psychiatric nurses, with an estimated 1–2 hours needed per patient and day of administration. This may temporarily reduce staff availability for other acute psychiatric interventions.

The treatment may impact work environment safety due to increased exposure to needlestick injuries.

Consequences for other clinics or supporting functions at the hospital or in Region Västra Götaland

Given the sparse evidence on the topic and the absence of comparisons with the clinically relevant treatment option ECT, potential consequences can only be speculated upon. If parenteral clomipramine were not available as a treatment option, the demand for ECT might increase, potentially requiring the expansion of ECT facilities, additional staff training, and increased allocation of anaesthesia resources.

11 Economic aspects

Available evidence only allows conclusions based on low certainty evidence for some of the critical and important outcomes and no evidence is available for the predefined relevant comparisons ECT and ketamine. Therefore, we restricted the cost calculations to drug costs during the first week of treatment, i.e., the week where costs differ, with either parenteral or oral clomipramine (Table 1).

The price of 1 ampoule (25 mg) clomipramine is 261.25 SEK. Using parenteral pulse loading in a regimen that is used clinically, the drug costs over the first week is estimated at 3,670 SEK. With gradual titration, the corresponding costs are 10,190 SEK. Oral treatment for one week amount to 43 SEK. It could be noted that the dose of oral clomipramine used in the cost calculations, due to its first-pass metabolism of about 50% and a metabolite which primarily inhibits noradrenalin reuptake, will result in lower serotonin reuptake inhibition compared with the corresponding dose of parenteral clomipramine.

Table 2 Doses and costs of parenteral clomipramine, using either pulse loading or gradual titration, and oral clomipramine over the first week of treatment

Clomipramine		**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Total costs (SEK)**
Parenteral, pulse loading	Dose	150 mg (6 amp)	200 mg (8 amp)	0 ml	0 ml	0 ml	150 mg PO	150 mg PO	
	Costs	**1,568**	**2,090**	**-**	**-**	**-**	**6.08**	**6.08**	**3,670**
Parenteral, gradual titration	Dose	50 mg (2 amp)	75 mg (3 amp)	100 mg (4 amp)	125 mg (5 amp)	175 mg (7 amp)	200 mg (8 amp)	225 mg (9 amp)	
	Costs	**523**	**784**	**1045**	**1,568**	**1,829**	**2,090**	**2,351**	**10,189**
Oral (75 mg tablets, Anafranil retard®)	Dose	150 mg	150 mg	150 mg	150 mg	150 mg	150 mg	150 mg	
	Costs	**6.08**	**6.08**	**6.08**	**6.08**	**6.08**	**6.08**	**6.08**	**43**

amp = ampoules, mg = milligram, ml = milliliter, PO = per os, SEK = Swedish crowns

12 Ethical aspects

As low certainty evidence did not show benefits of parenteral compared to oral clomipramine in patients with depression, and as infusion-related adverse events occurred, the benefit-risk balance may be negative. A negative benefit-risk balance for parenteral clomipramine may also apply to patients with OCD who have tried oral treatment without effect. For the comparisons with other treatments, the evidence was either uncertain or absent, preventing an evaluation of the benefit-risk balance.

From the perspective of equality and given that depression can have a very high severity and OCD a high severity, the needs and solidarity principle suggests that costly interventions may be acceptable. However, considering the potential absence of a positive benefit-risk balance of parenteral versus oral clomipramine combined with the higher costs of the former, the principle of cost-effectiveness may not be met. Regarding the prespecified relevant comparisons ECT and ketamine, no evidence was available, and the cost-effectiveness could therefore not be evaluated.

The principle of autonomy could be relevant for patients under compulsory care and for severely ill patients – informed decisions may be a challenge in these patient groups. However, parenteral clomipramine is in general not used in these patient groups.

13 Discussion

Summary of main results

This HTA systematically reviewed the efficacy and safety of parenteral clomipramine for patients with depression and OCD, focusing on comparisons with oral clomipramine, other treatments, and placebo. Fourteen RCTs fulfilled the PICO, with eleven addressing depression and three addressing OCD. For depression, based on low certainty of evidence, intravenous clomipramine may not be superior to oral administration in reducing depressive symptoms in the short or long term, but a clinically relevant effect cannot be excluded. Compared with placebo, low certainty of evidence shows that intravenous clomipramine may reduce depressive symptoms within two weeks; this conclusion was based on an RCT including adolescents for whom a 4-week washout for antidepressants was deemed acceptable. For OCD, the evidence is uncertain regarding potential differences between intravenous and oral clomipramine; based on low certainty evidence, intravenous clomipramine may not be superior to placebo in treatment-refractory cases. Across both indications, data on critical outcomes such as suicide attempts and all-cause mortality were lacking. Adverse events related to infusion were rare and generally consistent with known safety profiles, but the certainty of evidence was very low due to small sample sizes and few events.

It is important to note that these results specifically address the parenteral form of clomipramine, not clomipramine in general or TCAs as a drug class. In the included studies, a clinically relevant reduction in depressive and OCD symptoms was observed in most cases, regardless of administration route, consistent with previous literature on clomipramine and TCAs overall.

Overall completeness and applicability of evidence

For both studied conditions and especially for OCD, the certainty of evidence was limited by the small number and size of available RCTs. Furthermore, the RCTs were heterogenous regarding included patients and several RCTs had methodological limitations including unclear reporting of patient recruitment and the randomisation procedure. No RCT provided separate results for the HDRS item depressed mood which reportedly detects antidepressant effects more efficiently than the total HDRS score (Hieronymus et al., 2016).

The PICO of the current HTA intentionally implied a broad definition of depression that included both unipolar and bipolar subtypes without age restrictions. This approach reflects real-world clinical practice, aiming to capture the full spectrum of patients who might receive parenteral clomipramine in inpatient settings. Given available evidence, no subgroup analyses could be conducted based on the severity or subtype of depression, age, or the treatment condition (e.g., monotherapy vs. adjunctive treatment).

Most studies were conducted before the widespread use of modern antidepressants and under conditions that may not fully reflect current clinical practice. However, there is no clear evidence that the severity of depression among inpatients has markedly changed over the years (Fugger et al., 2020). While hospital admissions for moderate depression have risen, the number of severe cases and associated indicators like length of stay have remained relatively stable (Fugger et al., 2020; Sani et al., 2024). The recognition of comorbidities and their impact on severity has improved over time (Corruble et al., 2003; Sani et al., 2024; Popescu et al., 2024), but this has not translated into apparent shifts in the underlying severity profile of depression among inpatients. However, it is

important to note that Swedish studies on this topic are absent, and this aspect may be of importance for the generalisability of international findings.

Agreements and disagreements with other studies and reviews

The systematic review underlying the guidelines from the Swedish National Board of Health and Welfare, where TCA infusion is given low priority, was based on three studies, whereof two concerned parenteral clomipramine. One of the latter was a double-blind, double-dummy RCT that is also included in the present evidence synthesis (Pollock et al., 1989). The other was a non-randomised study (Faravelli et al., 1984). In patients with OCD, our results are consistent with a previous systematic review (Albert et al., 2018).

Implications for research

Given the sparsity of evidence and the severity of the conditions studied, further research with relevant comparisons can be considered highly warranted.

14 Future perspectives

Scientific knowledge gaps

Given the low certainty of evidence regarding potential effects on short-term and long-term depressive symptoms, with wide CIs that included the minimum clinically important difference; very low certainty of evidence for critical and important outcomes; and a total lack of evidence regarding the outcomes suicide attempts, all-cause mortality, suicidal ideation, global functioning, length of hospital stay, or health-related quality of life, there are evident knowledge gaps. Furthermore, the available RCTs did not study parenteral clomipramine as an alternative or adjunct to other rapid-acting interventions, such as ECT or ketamine, which are increasingly relevant in modern psychiatric care. These comparisons therefore represent important scientific knowledge gaps.

Ongoing research

The search in Clinicaltrials.gov resulted in 37 records. None of these fulfilled the PICO of this HTA.

15 Participants in the project

The question was nominated by

Mathias Alvidius, head of the Department of Psychiatry, Affective Disorders, Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Sweden

Participating healthcare professionals

Region Västra Götaland, Department of Psychiatry, Sahlgrenska University Hospital, Gothenburg, Sweden

- Michael Ioannou, MD, Senior consultant in psychiatry
- Örjan Falk, MD/PhD, Senior consultant in psychiatry
- Steinn Steingrimsson, MD/Associate Professor, Senior consultant in psychiatry
- Zóltan Szabó, MD/PhD, Senior consultant in psychiatry

Region Västra Götaland, Department of Clinical Pharmacology, Sahlgrenska University Hospital, Gothenburg, Sweden

- Johan Nilsson, MD/PhD, Resident in clinical pharmacology

Participants from HTA-centrum

Jahangir Khan, Professor of health economics
Petteri Sjögren, DDS/PhD
Susanna M Wallerstedt, MD/Professor, Senior consultant in clinical pharmacology

Participants from Medical Library

Joss Gustavsson, Librarian, Region Västra Götaland, Sahlgrenska University Hospital, Medical Library, Gothenburg, Sweden
Therese Svanberg, HTA-librarian, Region Västra Götaland, Sahlgrenska University Hospital, Medical Library, Gothenburg, Sweden

External reviewers

Harald Aiff, MD/PhD, Senior consultant in psychiatry
Anders Larsson, MD/PhD, Senior consultant in neurology

Declaration of interests

Örjan Falk, Joss Gustavsson, Michael Ioannou, Jahangir Khan, Petteri Sjögren, Therese Svanberg, Zoltan Szabo, and Susanna Wallerstedt have no conflicts of interest.

Steinn Steingrimsson has received consulting fees from a start-up company developing a computer game as an adjunctive treatment.

Johan Nilsson holds a part-time position at Clinical Trial Consultants (CTC) which is a clinical research organization (CRO) specializing on early-phase studies. He does not receive any direct compensation from the sponsor (e.g., a pharmaceutical company) and does not hold any ownership shares in CTC.

Project time

The HTA was accomplished during the period of 2024-09-18 to 2025-07-03.
Literature searches were conducted 2024-09-30.

Components of this Health Technology Assessment

- ✓ Description of methods
- ✓ PICO
- ✓ Full literature search
- ✓ Flowchart
- ✓ Selection based on relevance
- ✓ Quality assessment
- ✓ Data tabulation
- ✓ Evidence synthesis
- ✓ Meta-analysis
- ✓ Certainty of evidence by GRADE
- ✓ Summary
- ✓ Economical aspects
- ✓ Organisational aspects
- ✓ Ethical aspects
- ✓ Ongoing studies
- ✓ Excluded articles
- ✓ Participation of experts
- ✓ External review
- ✓ Knowledge gaps identified
- ✓ Conflict of interest reported

Appendix 1: PICO, study selection, search strategies, and references

Question(s) at issue
In patients with depression or OCD, is parenteral administration of clomipramine superior to oral clomipramine, other treatments, or placebo in terms of reducing depressive symptoms and obsessive-compulsive symptoms within two weeks, as well as other important outcome measures?

Patients (P)
P1: Patients with depression diagnosed in healthcare (unipolar and bipolar)
P2: Patients with OCD

Intervention (I)
I: Clomipramine via parenteral administration

Comparison (C)
C1: Clomipramine via other routes of administration (not parenterally)
C2: Other treatment (e.g. electroconvulsive therapy or other medication(s))
C3: Placebo

Outcomes (O)
Critical for decision-making

- Depressive symptoms (P1) or OCD symptoms (P2) within two weeks
- Suicide attempt
- All-cause mortality

Important for decision-making

- Long-term depressive symptoms (P1) or OCD symptoms (P2) (>2 weeks)
- Suicidal ideation
- Global functioning
- Treatment discontinuation
- Length of hospital stay
- Health-related quality of life (HROL)
- Adverse events related to administration via injection/infusion (e.g. thrombophlebitis, infection, anaphylaxis)

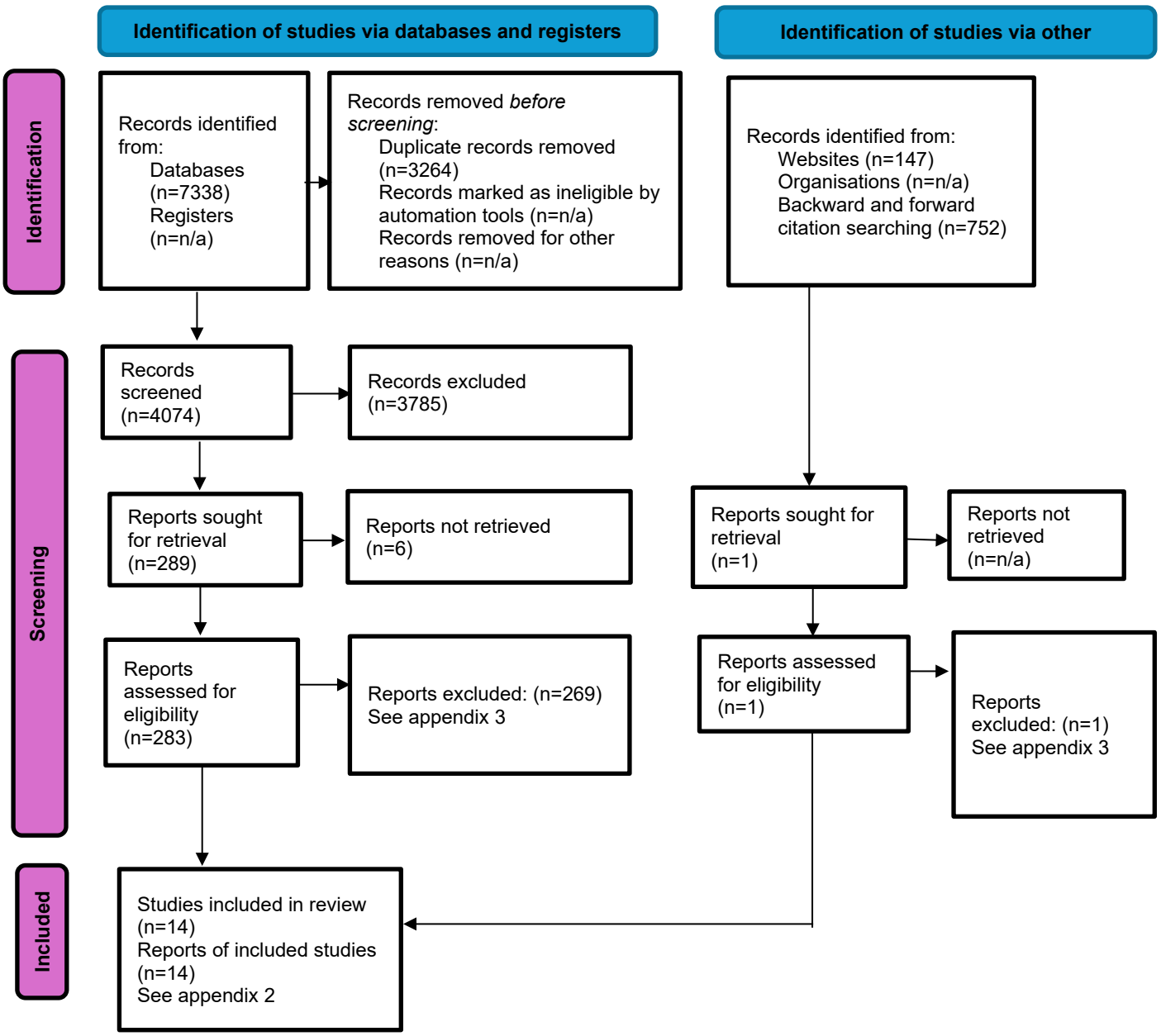
Restricted to:
Randomised controlled trials (RCT)
Studies written in English, Swedish, Danish or Norwegian

Predefined subgroup analyses
P: older patients (≥65 years); severe depression with melancholic or psychotic symptoms
I: Monotherapy; add-on therapy
C2: ECT; ketamine

The patient organisations “Balans” (depression) and “Ananke” (OCD) were asked to review the outcomes, and global functioning added thanks to the former.

Selection process – flow diagram

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



Search strategies

Database: Ovid MEDLINE(R) ALL
Date: 30 sep 2024
No. of results: 2,060

Search	Query	Items found
1	exp Clomipramine/	2,854
2	(chlorimipramine* or chlomipramine* or anafranil or hydiphen or clomipramine*).ab,kf,ti.	3,707
3	1 or 2	4,441
4	exp Mood Disorders/	175,487
5	exp Depression/	161,947
6	Compulsive Behavior/	3,553
7	Obsessive Behavior/	1,377
8	exp Obsessive-Compulsive Disorder/	18,198
9	(depress* or antidepress* or anti depress* or bipolar or obsessive or compulsive or OCD).ab,kf,ti.	723,436
10	4 or 5 or 6 or 7 or 8 or 9	781,746
11	3 and 10	3,156
12	animals/ not (animals/ and humans/)	5,228,303
13	(animal or animals or rat or rats or mouse or mice or rodent or rodents or dog or dogs or cat or cats or cow or cows or hamster or hamsters or koalas or rabbit or rabbits or swine or murine or porcine or horses or horse or goats or goat or cadaver or cadaveric).ti.	2,233,501
14	12 or 13	5,696,544
15	11 not 14	2,374
16	limit 15 to (danish or english or norwegian or swedish)	2,060

Database: Embase 1974 to 2024 September 27 (OvidSP)
Date: 30 sep 2024
No. of results: 3,300

#	Searches	Results
1	*clomipramine/	5,839
2	(chlorimipramine* or chlomipramine* or anafranil or hydiphen or clomipramine*).ab,kf,ti.	4,874
3	1 or 2	7,868
4	exp mood disorder/	727,861
5	exp obsessive compulsive disorder/	51,644
6	(depress* or antidepress* or anti depress* or bipolar or obsessive or compulsive or OCD).ab,	979,119
7	4 or 5 or 6	1,204,213
8	3 and 7	5,443
9	animal/ not (animal/ and human/)	1,230,833
10	(animal or animals or rat or rats or mouse or mice or rodent or rodents or dog or dogs or cat or cats or cow or cows or hamster or hamsters or koalas or rabbit or rabbits or swine or murine or porcine or horses or horse or goats or goat or cadaver or cadaveric).ti.	2,416,612
11	9 or 10	3,341,258
12	8 not 11	4,727

13	limit 12 to (danish or english or norwegian or swedish)	3,667
14	limit 13 to (embase or medline)	3,300

Database: The Cochrane Library
Date: 30 sep 2024
No of results: 658
Cochrane reviews: 13
Cochrane protocols: 0
Trials: 645

ID	Search	Hits
#1	MeSH descriptor: [Clomipramine] explode all trees	485
#2	(chlorimipramine* or chlomipramine* or anafranil or hydiphen or clomipramine*):ti,ab,kw (Word variations have been searched)	1015
#3	#1 OR #2	1015
#4	MeSH descriptor: [Mood Disorders] explode all trees	20524
#5	MeSH descriptor: [Depression] explode all trees	18683
#6	MeSH descriptor: [Compulsive Behavior] explode all trees	1128
#7	MeSH descriptor: [Obsessive Behavior] explode all trees	65
#8	MeSH descriptor: [Obsessive-Compulsive Disorder] explode all trees	1552
#9	(depress* or antidepress* or (anti NEXT depress*) or bipolar or obsessive or compulsive or OCD):ti,ab,kw (Word variations have been searched)	134152
#10	#4 OR #5 OR #6 OR #7 OR #8 OR #9	134771
#11	#3 AND #10	831
#12	(clinicaltrials OR trialsearch):so	535215
#13	(conference proceeding):pt	248848
#14	#12 OR #13	784063
#15	#11 NOT #14	757
Limit search to eng, dan, swe, nor		**658**

Database: PsycInfo
Date: 30 sep 2024
No. of results: 1,320

#	Query	Limiters/expanders	Results
S12	**S8 NOT 9**	Expanders - Apply related words; Apply equivalent subjects Narrow by: Academic journals Narrow by Language: - swedish Narrow by Language: - english	**1,320**

		Search modes - Find all my search terms	
S11	S8 NOT S9	Expanders - Apply related words; Apply equivalent subjects Narrow by Language: - swedish Narrow by Language: - english Search modes - Find all my search terms	1,383
S10	S8 NOT S9	Expanders - Apply related words; Apply equivalent subjects Search modes - Find all my search terms	1,594
S9	TI (animal OR animals OR rat OR rats OR mouse OR mice OR rodent OR rodents OR dog OR dogs OR cat OR cats OR cow OR cows OR hamster OR hamsters OR koalas OR rabbit OR rabbits OR swine OR murine OR porcine OR horses or horse OR goats OR goat OR cadaver OR cadaveric)	Expanders - Apply related words; Apply equivalent subjects Search modes - Find all my search terms	174,307
S8	S3 AND S7	Expanders - Apply related words; Apply equivalent subjects Search modes - Find all my search terms	1,817
S7	S4 OR S5 OR S6	Expanders - Apply related words; Apply equivalent subjects Search modes - Find all my search terms	452,525
S6	TI (depress* or antidepress* or "anti depress*" or bipolar or obsessive or compulsive or OCD) OR AB (depress* or antidepress* or "anti depress*" or bipolar or obsessive or compulsive or OCD)	Expanders - Apply related words; Apply equivalent subjects Search modes - Find all my search terms	436,620
S5	DE "Obsessive Compulsive Disorder" OR DE "Body Dysmorphic Disorder" OR DE "Excoriation Disorder" OR DE "Hoarding Disorder" OR DE "Koro" OR DE "Trichotillomania" OR DE "Compulsions" OR DE "Repetition Compulsion" OR DE "Obsessions" OR DE "Obsessive Compulsive Personality Disorder"	Expanders - Apply related words; Apply equivalent subjects Search modes - Find all my search terms	23,646
S4	DE "Major Depression" OR DE "Anaclitic Depression" OR DE "Dysthymic Disorder" OR DE "Endogenous Depression" OR DE "Late Life Depression" OR DE "Postpartum Depression" OR DE "Reactive Depression" OR DE "Recurrent Depression" OR DE "Seasonal Affective Disorder" OR DE "Treatment Resistant Depression" OR DE "Bipolar Disorder" OR DE "Bipolar I Disorder" OR DE "Bipolar II Disorder" OR DE "Cyclothymic Disorder" OR DE "Mania" OR DE "Bipolar I Disorder" OR DE "Bipolar II Disorder" OR DE "Depression (Emotion)" OR DE "Persistent Depressive Disorder" OR DE "Dysthymic Disorder"	Expanders - Apply related words; Apply equivalent subjects Search modes - Find all my search terms	231,522
S3	S1 OR S2	Expanders - Apply related words; Apply equivalent subjects Search modes - Find all my search terms	2,136
S2	TI (chlorimipramine* or chlomipramine* or anafranil or hydiphen or clomipramine*) OR AB (chlorimipramine* or chlomipramine* or anafranil or hydiphen or clomipramine*)	Expanders - Apply related words; Apply equivalent subjects Search modes - Find all my search terms	2,088
S1	DE "Chlorimipramine"	Expanders - Apply related words; Apply equivalent subjects	1,163

		Search modes - Find all my search terms	

The websites listed below were visited 25 Apr 2025.
Nothing relevant to the question at issue was found.

Source	Search terms / Browsing	No. of results	No. of relevant results
SBU www.sbu.se ”Visa även träffar äldre än 5 år”, Sortera på Rapporter	Klomipramin Depression Tvångssyndrom OCD	1 128 12 6	0 1 0 0
Folkehelseinstituttet (Norge) www.fhi.no	Browsat kategori Metodevurdering – Rapporter	0	0
Behandlingsrådet (Danmark) https://behandlingsraadet.dk/	Browsat	0	0
Nationale Kliniske Anbefalinger og Retningslinjer (Danmark) https://www.sst.dk/da/Fagperson/Retningslinjer-og-procedurer/NKA-og-NKR/NKR-og-NKA-efter-omraade	Browsat ämneskategori Mental sundhet samt Psykiske lidelser	0	0
CAMTÖ https://www.regionorebrolan.se/sv/forskning/kontakt-och-organisation/hta-enheten-camto/	Browsat	0	0
HTA Region Stockholm https://www.chis.regionstockholm.se/hta/rapporter/	Browsat	0	0
Regional samverkansgrupp HTA (tidigare Metodrådet) i Sydöstra sjukvårdsregionen https://sydostrasjukvardsregionen.se/samverkansgrupper/hta/genomforda-bedomningar/	Browsat	0	0
HTA Syd https://vardgivare.skane.se/kompetens-utveckling/sakkunniggrupper/hta-skane/#110365	Browsat	0	0
Vetenskapliga rådet, Region Dalarna https://www.regiondalarna.se/plus/vard/utveckling-och-utbildning/kunskapsstyrning/vetenskapliga-radet/	Browsat	0	0

Reference lists
A citation search in Web of Science (both backwards and forwards) of included articles resulted in 752 references.

Reference lists

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Project: Clomipramine parenterally
Appendix 2 Included articles

First author Year Country	Design (all RCTs)	Patients (n)	Age, years	Women (%)	Subgroups*	Intervention	Comparison	Outcome variables
P1: Patients with depression								
Altamura 2008 Italy	Single-blind, blinded raters	MDD/BPD with MDE, outpatients, cut-off symptom scores not defined I: 18 C2: 18 C3: 18	NR	40/54 (74%) Randomisation groups not separately reported	Add-on therapy: maintained on treatment with an SSRI	I: Clomipramine IV, 25 mg/day Treatment duration: 5 days	C2: Citalopram IV, 10 mg/day C3: saline Treatment duration: 5 days	Depressive symptoms within 2 weeks: HAM-D_{21} Treatment discontinuation
De Cuyper 1981 Belgium	Open label	Outpatients. recently hospitalised for vital depressive syndrome, cut-off symptom scores not defined I: 5 C1: 5	Range: I: 23–43 C1: 35–50	I: 3/5 C1: 3/5	Monotherapy (No other drugs allowed, apart from benzodiazepines as hypnotic)	I: Clomipramine IM, gradual titration, 25 mgx2 initially, after 2 days 50 mgx2. After 14 days, switch to oral daily dose of 200 mg administered in three separate doses Treatment duration: 4 weeks	C1: Clomipramine PO, 25 mgx3, with gradual increase to 200 mg daily on day 6 Treatment duration: 4 weeks	Depressive symptoms within 2 weeks: HRS, ZSRS Long-term depressive symptoms: HRS, ZSRS
Drago 1983 Italy	Double-blind	Hospitalised with severe primary depression (HDRS ≥18 or overt suicide tendency), treatment resistant (to 3 antidepressants over the previous 6 months I: 20	Mean (SD): I: 49.35 (10.43) C2: 48.45 (13.12)	I: 20/20 C2: 20/20	NR	I: Clomipramine IV, 100 mg daily Treatment duration: 21 days (9 days if non-responder, thereafter cross-over)	C2: Maprotiline IV, 100 mg daily Treatment duration: 21 days (9 days if non-responder, thereafter cross-over)	Depressive symptoms within 2 weeks: $HDRS_{17}$ (Long-term depressive symptoms reported as above, but non-responders crossed over after 9 days and the results are therefore not relevant.)

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Appendix 2 Included articles

First author Year Country	Design (all RCTs)	Patients (n)	Age, years	Women (%)	Subgroups*	Intervention	Comparison	Outcome variables
		C2: 20						
Escobar 1973 US	Double-blind, double dummy	Patients with "target symptom of depression", HDS: ≥25 I: 14 C1: 17 (After dropouts (NR) were replaced)	Range: 20–64 Mean: 43 Randomisation groups not reported separately. Described as "similar".	I: 9/14 C1: 9/17	NA	Day 1–10: I: Clomipramine IV, 25–150 mg (gradual titration not explicitly described) Day 11-21: Clomipramine PO, 75–300 mg	Day 1–10: C1: Clomipramine PO, 75–300 mg (gradual titration not explicitly described) Day 11-21: Clomipramine PO, 75–300 mg	Depressive symptoms within 2 weeks: HDS, ZSRS Long-term depressive symptoms: HRS, ZSRS Adverse events related to administration via injection/infusion
Faravelli 1983 Italy	Double-blind, double dummy	Inpatients, major depressive disorder, primary subtype, HRS: ≥18 after wash-out 5-7 days I: 20 C1: 20	Mean (SD): I: 56.3 (9.8) C1: (58.2 (11.4)	I: 13/20 C1: 13/20	Monotherapy (No other drugs allowed, apart from occasional lorazepam)	I: Clomipramine IV, gradual titration, 0.5 g/kg every 3 days, maximum 2 mg/kg, maintained dose from day 10 Treatment duration: 4 weeks	C1: Clomipramine PO, gradual titration, 0.5 g/kg every 3 days, maximum 2 mg/kg, maintained dose from day 10 Treatment duration: 4 weeks	Depressive symptoms within 2 weeks: HRS Long-term depressive symptoms: HRS Treatment discontinuation Adverse events related to administration via injection/infusion
Fähndrich 1983 Germany	Open label	Depression requiring medication, wash-out 4 days, after which sleep deprivation was carried out I: 30 C2: 30	Mean (range) I: 49.9 (28–72) C2: 54.6 (20–75)	I: 24/30 C2: 21/30	Monotherapy (Performed after wash-out)	I: Clomipramine IV, gradual titration, 75 mg/day for 3 days, subsequently 100 mg/day Treatment duration: 3 weeks	C2: Maprotiline IV, gradual titration, 75 mg/day for 3 days, subsequently 100 mg/day Treatment duration: 3 weeks	Long-term depressive symptoms: HRS

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Appendix 2 Included articles

First author Year Country	Design (all RCTs)	Patients (n)	Age, years	Women (%)	Subgroups*	Intervention	Comparison	Outcome variables
Hordern 1979 UK	Double-blind, double dummy	Part I: Inpatients, primary depressive state I: 20 C1: 15 Part II: Outpatients I: 9 C1: 6	Mean (SD) Part I: I: 46 (15) C1: 48 (15) Part II I: 44 (13) C1: 49 (5)	Part I (Completers) I: 11/15 C1: 8/12 Part II (Completers) I: 7/8 C1: 2/4	Monotherapy (diazepam, chlorpromazine, and nitrazepam kept to a minimum)	I: Clomipramine IV, gradual titration, from 50 to 125 mg/day (four days a week) Treatment duration: 4 weeks	C1: Clomipramine PO, gradual titration, from 75 to 150 mg/day (daily) Treatment duration: 4 weeks	Depressive symptoms within 2 weeks: HRS Long-term depressive symptoms: HRS Treatment discontinuation Adverse events related to administration via injection/infusion
Lecrubier 1980 France	Single-blind (blinded raters)	Inpatients with depressive syndrome (uni- and bipolar) I: 10 C2: 10	Mean I: 50.8 C2: 45.8	I: 6/10 C2: 6/10	Monotherapy (diazepam, nitrazepam, levomepromazine allowed)	I: Clomipramine IV, gradual titration, day 1: 75 mg, day 2: 100 mg, thereafter 150 mg/day Treatment duration: 15 days	C2: Salbutamol IV, gradual titration, from 1.5 mg to 3 mg/infusion twice daily, i.e., 6 mg a day Treatment duration: 15 days	Depressive symptoms within 2 weeks: HRS Long-term depressive symptoms: HRS
Pollock 1989 US	Double-blind, double dummy	Inpatients with major depressive disorder (unipolar), HAM-D_{17} ≥15. Initial two-week drug-free period I: 11 C1: 11	Mean (SD) I: 34 (7) C1: 42 /11)	I: 10/11 C1: 8/11	Monotherapy	I: Clomipramine IV, pulse loaded, day 1: 150 mg, day 2: 200 mg, day 3–7: no treatment, day 8–28: clomipramine PO, 200 mg, adjustable	C1: Clomipramine PO, pulse loaded, day 1: 150 mg, day 2: 200 mg, day 3–7: no treatment, day 8–28: clomipramine PO, 200 mg, adjustable	Depressive symptoms within 2 weeks: HAM-D_{17} Long-term depressive symptoms: HAM-D_{17} Treatment discontinuation
Sallee 1997 US	Double-blind	Adolescents (14–18 years), outpatients, major depression. Initial 4-week washout for	Mean (SD) I: 16.1 (0.9) C3: 16.4 (1.0)	I: 2/8 C3: 3/8	Monotherapy	I: Clomipramine IV, pulse load, day 1: 200 mg, no further infusions	C3: Saline placebo, day 1: infusion, not further infusions	Depressive symptoms within 2 weeks: HAM-D_{21},, BDI, CGI-S

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Appendix 2 Included articles

First author Year Country	Design (all RCTs)	Patients (n)	Age, years	Women (%)	Subgroups*	Intervention	Comparison	Outcome variables
		antidepressant (6 weeks for fluoxetine) I: 8 C3: 8						
Spreux-Varoquaux 1996 France	Double-blind, double dummy	Nondeluded depressed inpatients (unipolar), MADRS ≥20. 7-day washout for antidepressants required. I: 13 C1: 14	Mean (SD) I: 50.5 (3.0) C1: 38.9 (2.2)	I: 9/13 C1: 11/14	Monotherapy (chlorzepate allowed)	I: Clomipramine IV, gradual titration, from 25 to 75 mg/day (day 3–14: 75 mg/day) Treatment duration: 14 days	C1: Clomipramine PO, gradual titration, from 50 to 150 mg/day (day 3–14: 150mg/day) Treatment duration: 14 days	Depressive symptoms within 2 weeks: MADRS

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Appendix 2 Included articles

First author Year Country	Design (all RCTs)	Patients (n)	Age, years	Women (%)	Subgroups*	Intervention	Comparison	Outcome variables
P2: Patients with OCD								
Fallon 1998 US	Double-blind	OCD poorly responsive to clomipramine PO, Y-BOCS >16 I: 29 C3: 25	Mean (SD): 32.4 (9) Randomisation groups not reported separately.	33/54 Randomisation groups not reported separately.	Monotherapy (2-week washout, 4 weeks for fluoxetine)	I: Clomipramine IV, gradual increments: 25 mg/day for 8 days, thereafter 250 mg Treatment duration: 14 weekdays	C3: Placebo Treatment duration: 14 weekdays	OCD symptoms within 2 weeks: Y-BOCS, CGI-S (Placebo group allowed clomipramine IV after 2 weeks)
Koran 1997 US	Double-blind, double dummy	OCD, Y-BOCS ≥17 I: 7 C1: 8	Mean (SD) I: 33.4 (4.3) C1: 29.1 (4.3)	I: 1/7 C1: 1/8	Trimethobenzamide administered before first dose	I: Clomipramine IV, pulse loaded, day 1: 150 mg, day 2: 200 mg, from 4.5 days after the second dose: 150 mg PO with increases of 25 mg/day to a maximum of 250 mg Treatment duration: 8 weeks	C1: Clomipramine PO, pulse loaded, day 1: 150 mg, day 2: 200 mg, from 4.5 days after the second dose: 150 mg PO with increases of 25 mg/day to a maximum of 250 mg Treatment duration: 8 weeks	OCD symptoms within 2 weeks: Y-BOCS Long-term OCD symptoms: Y-BOCS
Koran 2006 US	Double-blind, double dummy	OCD, Y-BOCS ≥20, failed 2 SRIs I: 16 C1: 16	Randomisation groups NR	16/32 Randomisation groups not reported separately	Monotherapy	I: Clomipramine IV, pulse loaded, day 1: 150 mg, day 2: 200 mg, from day 6: 200 mg/day PO, increased to 250 mg/day if tolerated Treatment duration: 12 weeks	C1: Clomipramine PO, pulse loaded, day 1: 150 mg, day 2: 200 mg, from day 6: 200 mg/day PO, increased to 250 mg/day if tolerated Treatment duration: 12 weeks	OCD symptoms within 2 weeks: Y-BOCS Long-term OCD symptoms: Y-BOCS Treatment discontinuation Adverse events related to administration via injection/infusion

BDI = Beck depression, inventory scale, BPD = bipolar disorder, C = comparison, C1: clomipramine non-parenterally, C2: other treatment for the condition, C3: placebo, CGI-S = Clinical global impression severity scale, HADS = Hamilton depression scale, $HAM\text{-}D_{17}$= Hamilton depression rating scale, 17 items, $HAM\text{-}D_{21}$ = Hamilton depression rating scale, 21 items, $HDRS_{17}$ = Hamilton depression rating scale, first 17 items, HDS = Hamilton depression scale, HRS = Hamilton rating scale, I = intervention, IM = intramuscular, IV = intravenous, MADRS = Montgomery-Åsberg Depression Rating Scale, MDD = major depressive disorder, MDE = major depressive episode, NA =

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Appendix 2 Included articles

First author Year Country	Design (all RCTs)	Patients (n)	Age, years	Women (%)	Subgroups*	Intervention	Comparison	Outcome variables

not applicable, NR = not reported, PO = per os, RCT = randomised controlled trial, SD = standard deviation, SRI = serotonin reuptake inhibitor, UK = United Kingdom, US = United States, Y-BOCS = Yale-Brown obsessive compulsive scale, ZSRS = Zung self-rating scale
*Predefined subgroups: P: older patients (≥65 years), I: Monotherapy or add-on therapyC2: ECT or ketamine

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Appendix 3.
Excluded articles

Author, year	Reason for exclusion
Abu-Naser, 2021	Wrong intervention: No mention of intravenous clomipramine
Ackerman, 2002	Wrong intervention: No mention of intravenous clomipramine
Ahmadpanah, 2017	Wrong intervention: Buprenorphine
Alarcon, 1993	Wrong study design: Case-series. No mention of intravenous clomipramine
Albert, 2018	Systematic review with many interventions, intravenous clomipramine mentioned briefly but no results
Alqdwah-Fattouh, 2020	Wrong study design: Nested case-control. No mention of intravenous clomipramine.
Amin, 1977	Wrong intervention: Oral administration
Amsterdam, 1997	Wrong intervention: No mention of intravenous clomipramine
Ananth, 1977	Wrong intervention: Oral administration
Bandelow, 2023	Wrong publication type: Guideline
Beaumont, 1974	Wrong publication type: Conference abstract
Bech, 1984	Wrong intervention: No mention of intravenous clomipramine
Becker, 1971	Wrong study design: Non-randomised study
Berman, 1995	Wrong intervention: No mention of intravenous clomipramine
Bertolin, 2021	Wrong study design: Systematic review (”intravenous” not mentioned)
Boaden, 2020	Systematic review of systematic reviews: No mention of intravenous clomipramine
Buchholtz-Hansen, 1993	Wrong intervention: No mention of intravenous clomipramine
Buoli, 2019	Wrong study design: Non-randomised study
Burnand, 2002	Wrong intervention: No mention of intravenous clomipramine
Carvajal Garcia-Pando, 2002	Wrong study design, wrong intervention: No mention of intravenous clomipramine
Cassano, 1981	Wrong intervention: Oral administration
Ceskova, 1981	Wrong study design: Non-randomised study
Chistyakov, 2005	Wrong intervention: No mention of intravenous clomipramine
Choi, 2009	Wrong intervention: No mention of intravenous clomipramine
Christensen, 1985	Wrong intervention: No mention of intravenous clomipramine
Cipriani, 2016	Wrong intervention: No mention of intravenous clomipramine. Many different treatments
Cipriani, 2018	Wrong intervention: No mention of intravenous clomipramine. Many different treatments
Civeira, 1990	Wrong intervention: Oral administration

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Excluded articles

Author, year	Reason for exclusion
Cohen, 2024	Wrong study design: Systematic review (”intravenous” not mentioned)
Collins, 1970	Wrong study design: Case series
Collins, 1973	Wrong study design: Non-randomised study
Cordes, 2009	Wrong study design: Non-randomised study
de Oliveira, 2023	Wrong publication type: Guideline
Degner, 2004	Wrong publication type
Della Corte, 1979	Wrong study design: Non-randomised study
Dencker, 1976	Wrong study design: Non-randomised study
Desaunay, 2024	Wrong study design: systematic review (”intravenous” not mentioned)
DeVeaugh-Geiss, 1992	Wrong intervention: Oral administration
Dierick, 1990	Wrong intervention: No mention of intravenous clomipramine
Dimitriou, 1984	Wrong intervention: No mention of intravenous clomipramine
Diniz, 2010	Wrong intervention: Oral administration
Eddy, 2004	Wrong publication type: Meta analysis. No mention of intravenous clomipramine
Ehlers, 1996	Wrong study design: Case series
Elsenga, 1982	Wrong intervention: No mention of intravenous clomipramine
Elsenga, 1987	Wrong intervention: No mention of intravenous clomipramine
Erzegovesi, 2001	Wrong intervention: Oral administration
Escobar, 1976	Wrong study design: Case series
Escobar, 1977	Wrong study design: Case series
Ewald, 1971	Wrong study design: Case series
Faravelli, 1983b	Wrong study design: Non-randomised study
Faravelli, 1987	Wrong publication type: Some kind of non-systematic review
Faravelli, 1987	Wrong publication type, also duplicate
Farhat, 2020	Systematic review with many interventions, no mention of intravenous clomipramine
Feng, 2007	Wrong intervention: Oral administration
Feng, 2016	Wrong intervention: Oral administration
Fineberg, 2007	Wrong publication type: systematic review with no mention of intravenous clomipramine

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Excluded articles

Author, year	Reason for exclusion
Flament, 1985	Wrong intervention: Oral administration
Fountain, 2020	Wrong publication type, registry data, no mention of intravenous clomipramine
Friedrich, 2016	Wrong publication type, registry data, no mention of intravenous clomipramine
Friedrich, 2022	Wrong publication type, registry data, no mention of intravenous clomipramine
Fuglum, 1996	Wrong intervention: No mention of intravenous clomipramine
Funke, 1990	Wrong intervention: Oral administration
Fähndrich, 1983	Wrong study design: Non-randomised study
Fähndrich, 1987	Results according to our PICO presented in Fähndrich 1983 (included studies), no additional data presented
Geller, 2003	Wrong publication type, no mention of intravenous clomipramine
Gentile, 2011	Wrong publication type, no mention of intravenous clomipramine
Gex-Fabry, 1999	Wrong study design: Case series
Golden, 1992	Wrong study design: Non-randomised study
Golden, 2002	Wrong study design: Non-randomised study
Gorenstein, 2006	Wrong intervention: No mention of intravenous clomipramine
Grant, 2013	Wrong study design: Non-randomised study. Wrong focus
Greil, 2019	Wrong intervention: No mention of intravenous clomipramine
Greist, 1990	Wrong intervention: No mention of intravenous clomipramine
Greist, 1995	Too old (meta-analysis 1995). No mention of intravenous clomipramine
Grohmann, 1993	Wrong intervention: No mention of intravenous clomipramine
Grohmann, 2004	Wrong intervention: No mention of intravenous clomipramine
Guyotat, 1969	Wrong language: French
Haghighi, 2013	Wrong intervention: No mention of intravenous clomipramine
Hansen, 1994	Wrong intervention: No mention of intravenous clomipramine
Hembree, 2003	Wrong intervention: No mention of intravenous clomipramine
Hessov, 1969	Wrong study design: Case series
Hewlett, 1992	Wrong intervention: No mention of intravenous clomipramine
Hoehn-Saric, 1993	Wrong intervention: No mention of intravenous clomipramine
Hoffman, 2021	Wrong publication type: Review, no mention of intravenous clomipramine

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Author, year	Reason for exclusion
Hojaij, 1995	Wrong study design: Case series
Holper, 2020	Meta-analysis with no mention of intravenous clomipramine
Hsu, 1995	Wrong study design: Case series
Humble, 2001	Wrong intervention: No mention of intravenous clomipramine
Humble, 2013	Wrong intervention: No mention of intravenous clomipramine
Humble, 2016	Wrong intervention: No mention of intravenous clomipramine
Insel, 1983	Wrong intervention: D-amphetamine
Insel, 1983	Wrong intervention: Oral administration
Jarrett, 1991	Wrong study design: Case series
Jenike, 1989	Wrong intervention: Oral administration
Jenike, 1990	Old meta-analysis with no mention of intravenous clomipramine
Johnco, 2020	Wrong publication type: Meta-analysis, no mention of intravenous clomipramine
Johnson, 1985	Wrong intervention: No mention of intravenous clomipramine
Jouvent, 1998	Wrong intervention: No mention of intravenous clomipramine
Joyce, 1994	Wrong intervention: Oral administration
Jörgensen, 1984	Wrong intervention: Oral administration
Karameh, 2015	Wrong study design: Case series
Kasvikis, 1988a	Wrong intervention: Oral administration
Kasvikis, 1988b	Wrong intervention: No mention of intravenous clomipramine
Katz, 1990a	Wrong publication type, no mention of intravenous clomipramine
Katz, 1990b	Wrong intervention: No mention of intravenous clomipramine
Kessing, 2024	Wrong intervention: No mention of intravenous clomipramine
Khan, 2004	Wrong intervention: No mention of intravenous clomipramine
Khanna, 1988	Wrong intervention: No mention of intravenous clomipramine
Klicpera, 1979	Wrong study design: Non-randomised study
Klok, 1981	Wrong intervention: Oral administration
Koran, 1998	Wrong I/C: Pulse loading vs gradual dosing of intravenous clomipramine
Kornhaber, 1984	Wrong intervention: Oral administration

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Author, year	Reason for exclusion
Koszewska, 2009	Wrong intervention, many different treatments, no mention of intravenous clomipramine
Kundermann, 2009	Wrong intervention. Focus on sleep deprivation therapy
Kupfer, 1994	Wrong intervention: Oral administration
Kuss, 1986	O missing: Focus on pharmacokinetics. Unclear randomisation
Landeros-Weisenberger, 2010	Wrong intervention: No mention of intravenous clomipramine. Wrong publication type
Langer, 1983	Wrong study design: Non-randomised study
Langer, 1984	Wrong study design: Non-randomised study
Langer, 1986	Wrong study design: Non-randomised study
Larisch, 2003	Wrong P: Patients with depression in remission
Larsen, 1984	Wrong study design: Case report
Lax, 1992	Wrong intervention: No mention of intravenous clomipramine
Lechin, 1983	Wrong intervention: No mention of intravenous clomipramine
Lejoyeux, 1993	Wrong intervention: Oral administration
Leonard, 1995	Wrong publication type, no mention of intravenous clomipramine
Leonard, 1988	Wrong intervention: Oral administration
Leth-Moller, 2016	Wrong study design, register study. No mention of intravenous clomipramine
Licht, 2013	Wrong intervention: Oral administration
Limosin, 2006	Wrong intervention: Oral administration
Linder, 1989	Wrong intervention, oral administration
Lykouras, 2011	Wrong study design: Non-randomised study
Ma, 2013	Wrong intervention: No mention of intravenous clomipramine
Madalena, 1968	Wrong language: Spanish
Maina, 2004	Wrong study design: Non-controlled study
Mao, 2022	Wrong study design: Systematic review (”intravenous” not mentioned)
Marazziti, 1997	Wrong intervention: No mention of intravenous clomipramine
March, 1990	Wrong intervention: Oral administration
Margat, 1969	Wrong language: French
Marks, 1988	Wrong intervention: Oral administration

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Excluded articles

Author, year	Reason for exclusion
Marshall, 1975	Wrong study design: Case series
Mathew, 2001	Wrong study design: Case series
Mavissakalian, 1985	Wrong intervention: No mention of intravenous clomipramine
Mavissakalian, 1990	Wrong intervention: No mention of intravenous clomipramine
Mawson, 1982	Wrong intervention: No mention of intravenous clomipramine
McClure, 1973	Wrong intervention: No mention of intravenous clomipramine
McGuire, 2014	Wrong focus/Wrong intervention: Many different treatments, no mention of intravenous clomipramine
Merino, 2000	Wrong intervention: No mention of intravenous clomipramine
Miccoli, 1978	Wrong study design: Non-randomised study
Milanfranchi, 1997	Wrong intervention: No mention of intravenous clomipramine
Miller, 1995	Wrong intervention: No mention of intravenous clomipramine
Minelli, 2010	O missing: Motor excitability
Monteiro, 1987	Wrong intervention: Oral administration.
Montejo, 2001	Wrong intervention: Many different treatments, no mention of intravenous clomipramine
Montgomery, 2001	Wrong focus/Wrong study design
Moukaddam, 2004	Wrong study design, no systematic review
Moyes, 1980	Wrong intervention: No mention of intravenous clomipramine
Mumoli, 2014	Wrong study design: Case-series. No treatment with intravenous clomipramine
Mundo, 1995	C missing: All patients received intravenous clomipramine
Mundo, 1999	C missing: All patients received intravenous clomipramine
Mundo, 2000	Wrong intervention: Oral administration
Mundo, 1997	Wrong intervention: Oral administration
Murphy, 1975	Wrong intervention: Oral administration
Murphy, 1977	Wrong intervention: Oral administration
Müller-Oerlinghausen, 1985	Results according to our PICO presented in Fähndrich 1983 (included studies), no additional data presented
Möller, 1984	Wrong intervention: Oral administration
Möller, 1990	Wrong intervention: Oral administration
Nagayama, 1991	Wrong intervention: Oral administration

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Excluded articles

Author, year	Reason for exclusion
Nahunek, 1984	Wrong study design: Non-randomised study
Nielsen, 1990	Wrong intervention: Oral administration
Ninan, 2000	Wrong intervention: Oral administration
Noguera, 1991	Wrong intervention: Oral administration
O'Flanagan, 1974	Wrong publication type: Conference abstract
O'Sullivan, 1991	Wrong intervention: Oral administration
Okayasu, 2012	Wrong focus/Wrong intervention: No mention of intravenous clomipramine
Okayasu, 2019	Wrong focus/Wrong intervention: No mention of intravenous clomipramine
Orgeta, 2017	Wrong population: Alzheimer and depression. No mention of intravenous clomipramine
Pahus, 1970	Wrong intervention: Oral administration
Pallanti, 1999	Wrong intervention: Oral administration
Pandey, 2020	Wrong intervention: Oral administration
Pato, 1988	Wrong intervention: Oral administration
Pato, 1991	Wrong intervention: Oral administration
Perroud, 2011	Wrong intervention: No mention of intravenous clomipramine
Persson, 2007	Wrong study design: Case series
Perugi, 2002	Wrong focus/Wrong intervention: No mention of intravenous clomipramine
Pigott, 1990	Wrong intervention: Oral administration
Pigott, 1991	Wrong intervention: Oral administration
Pigott, 1992	Wrong intervention: Oral administration
Pinder, 1980	Wrong intervention: Oral administration
Pinkava, 1974	Wrong study design: Non-randomised study
Pizarro, 2014	Review with literature in only one database, no relevant studies on clomipramine
Pollock, 1993	Wrong I/C: Pulse loading vs gradual dosing of intravenous clomipramine
Pollock, 1986	Wrong study design: Case series
Porter, 2003	Wrong intervention: No mention of intravenous clomipramine
Quilty, 2010	Wrong intervention: No mention of intravenous clomipramine
Rabe-Jablonska, 2001	Wrong comparison: Healthy volunteers. Wrong study design: non-randomised study

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Excluded articles

Author, year	Reason for exclusion
Rachman, 1979	Wrong intervention: No mention of intravenous clomipramine
Rack, 1977	Wrong study design: Case series
Rapisarda, 1982	Wrong intervention: Oral administration.
Rapoport, 1980	Wrong intervention: No mention of intravenous clomipramine
Ravizza, 1995	Wrong intervention: No mention of intravenous clomipramine
Revet, 2020	Wrong publication type, registry data, no mention of intravenous clomipramine
Riemann, 1990	Wrong intervention: No mention of intravenous clomipramine
Ross, 2008	Wrong study design: Case series
Rothbart, 2013	Too old/Duplicate (See Hoffmann - same title)
Sallee, 1998	Wrong study design: Randomised and non-randomised patients included, randomised patients not reported separately
Sallee, 1998	Wrong study design: Non-randomised study
Sallee, 1989	Wrong study design: Case series
Sanchez-Meca, 2014	Systematic review with several different treatments, no mention of intravenous clomipramine
Scarzella, 1985	Wrong intervention: No mention of intravenous clomipramine
Schlienger, 2004	Wrong study design: Case-control. No mention of intravenous clomipramine
Schoretsanitis, 2020	Wrong focus/Wrong intervention: Different antidepressants, no mention of intravenous clomipramine
Sepulveda-Lizcano, 2023	Wrong focus/Wrong intervention: Different treatments, no mention of intravenous clomipramine
Serna, 2010	Wrong focus/Wrong intervention: No mention of intravenous clomipramine
Shaw, 1975	Wrong intervention: No mention of intravenous clomipramine
Silva, 1976	Wrong intervention: Oral administration
Singer, 1968	Wrong language: French
Skapinakis, 2016	Wrong focus/Wrong intervention: Several different treatments
Skapinakis, 2016	Wrong focus/Wrong intervention: Several different treatments
Skapinakis, 2021	Reprint
Slikboer, 2017	Wrong focus/Wrong intervention, several different treatments, no mention of intravenous clomipramine
Soomro, 2012	Wrong focus/Wrong intervention, several different treatments, no mention of intravenous clomipramine
Souetre, 1996	Wrong intervention: No mention of intravenous clomipramine
Souetre, 1997	Wrong intervention: No mention of intravenous clomipramine

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Author, year	Reason for exclusion
Statens beredning för medicinsk och social utvärdering (SBU), 2004	Several different treatments, no mention of intravenous clomipramine
Steinert, 2018	Review with literature in only one database, no relevant studies on clomipramine
Stern, 1980	Wrong intervention: No mention of intravenous clomipramine
Suchting, 2021	Wrong focus/Wrong intervention: No mention of intravenous clomipramine
Swedo, 1989	Wrong intervention: Oral administration
Szegedi, 1996	Wrong intervention: No mention of intravenous clomipramine
Szymanska, 2001	Wrong publication type: Non-randomised controlled trial
Tao, 2022	Wrong focus/Wrong intervention: Several different treatments, no mention of intravenous clomipramine
Taylor, 2024	Review with literature in only one database, no relevant studies on clomipramine
Thoren, 1980	Wrong intervention: Oral administration
Uguz, 2019	Wrong focus/Wrong intervention: Several different treatments, no mention of intravenous clomipramine
Uguz, 2021	Wrong focus/Wrong intervention: Several different treatments, no mention of intravenous clomipramine
Ulrich, 1988	Substudy of Fähndrich 1983 with EEG focus, no additional data according to our PICO presented
Ulrich, 1994	O missing: EEG
van Kammen, 1980	Wrong study design: Case series. Wrong comparison
van Scheyen, 1977	Wrong intervention: Oral administration
Van Scheyen, 1979	Wrong study design: No comparison of results
van Soest, 2007	Wrong intervention: No mention of intravenous clomipramine
Varigonda, 2016	Wrong focus/Wrong intervention: Several different treatments, no mention of intravenous clomipramine
Veale, 2014	Wrong intervention: Several different treatments, no mention of intravenous clomipramine
Vencovsky, 1971	Wrong study design: Case series
Vestergaard, 2008	Wrong study design: Case-control. Wrong intervention, association several SSRI and risk of fracture, no mention of intravenous clomipramine
Viktorin, 2017	Wrong intervention: Several different treatments, no mention of intravenous clomipramine
Voican, 2016	Wrong focus/Wrong intervention: Several different treatments, no mention of intravenous clomipramine
Volavka, 1985	Wrong intervention: Oral administration
Volmat, 1968	Wrong language: French

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Author, year	Reason for exclusion
Von Oefele, 1986	Wrong study design. Wrong intervention: Tricyclic and MAOI therapy, no mention of intravenous clomipramine
Vos, 2023	Wrong intervention: No mention of intravenous clomipramine
Warneke, 1992	Wrong publication type: Comment
Waxman, 1977	Wrong intervention: Oral administration
Wilson, 2004	Wrong focus/Wrong intervention: Several different treatments, no mention of intravenous clomipramine
Winkler, 2021	Wrong study design: Drug surveillance report, no mention of intravenous clomipramine
Wyndowe, 1975	Wrong intervention: Oral administration
Wålinder, 1976	Wrong intervention: No mention of intravenous clomipramine
Wålinder, 1981	Wrong intervention: No clomipramine
Xiong, 2006	Wrong focus: Several different treatments, no mention of intravenous clomipramine
Xu, 2021	Wrong study design: Systematic review (”intravenous” not mentioned)
Yamada, 2003	Wrong intervention: No mention of intravenous clomipramine
Younus, 2024	Review with literature in only one database, no relevant studies on clomipramine
Zahn, 1984	Wrong intervention: No mention of intravenous clomipramine
Zapletalek, 1982	Wrong study design: Case series
Zhao, 1991	Wrong language: Chinese
Zhou, 2024	Systematic review, several different treatments, no mention of intravenous clomipramine
Zohar, 1988	Wrong intervention: oral administration
Zohar, 1996	Wrong intervention: oral administration

* + No or minor problems
? Some problems
- Major problems

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Appendix 4.1
Outcome variable: Depressive/OCD symptoms within 2 weeks

Author Year Country	Patients	Withdrawals - dropouts	Results		Comments	Directness*	Risk of bias*[1]	Precision*
			Intervention	Comparison				
-10P1: Patients with depression								
Altamura 2008 Italy	I: 18 C2: 18 C3: 18	0 (NR)	*HAM-D_{21}*[2] Change in scores, mean I: -11 (Initial score: 20) Response: ≥50% decrease I: 11/18 Remission I: 9/18	*HAM-D_{21}*[2] Change in scores, mean C2: -12 (initial score: 24) C3: -2.5 (initial score: 20) Response: ≥50% decrease C2: 9/18 C3: 0/18 Remission C2: 3/18 C3: 0/18	Day 5 HAM-D_{21} score changes estimated from figure	-	-	?
De Cuyper 1981 Belgium	I: 5 C1: 5	0 (HRS) 1 (ZSRS)	*HRS*[2] Change in scores, mean (SD) [improvement in percentage] I: -7.2 (4.6) [19%] Response: ≥50% decrease I: 0/5 *ZSRS* Change in scores, mean (SD) I: -4.8 (4.4)	*HRS*[2] Change in scores, mean (SD) [improvement in percentage] C1: -9 (3.5) [32%] Response: ≥50% decrease C1: 0/5 *ZSRS* Change in scores, mean (SD) C1: -2.6 (7.7)	Week 2 HRS and ZSRS absolute scores NR	?	-	-
Drago 1983 Italy	I: 20 C2: 20	0 (NR)	*$HDRS_{17}$*[2] Change in scores, mean (SD) $I_{day\ 5}$: -7.25 (8.08)$_{day\ 5}$, -12.25 (10.59)$_{day\ 9}$ (Initial score: 25.4 (5.41) *Global evaluation of severity of the disease, VAS 0-100* Responder (≥50% improvement) I: 4/20$_{day\ 5}$, 9/20$_{day\ 9}$	*$HDRS_{17}$*[2] Change in scores, mean (SD) C2: -5.1 (5.92)$_{day\ 5}$, -7.8 (9.83)$_{day\ 9}$ (Initial score: 26.6 (6.41)) *Global evaluation of severity of the disease, VAS 0-100* Responder (≥50% improvement) C2: 1/20$_{day\ 5}$, 6/20$_{day\ 9}$	Days 5 & 9	?	+/?	?

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? Some problems
- Major problems

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Appendix 4.1
Outcome variable: Depressive/OCD symptoms within 2 weeks

Author Year Country	Patients	Withdrawals - dropouts	Results		Comments	Directness*	Risk of bias*[1]	Precision*
			Intervention	Comparison				
Escobar 1973 US	I: 14 C: 17	"dropouts replaced", not further described	*HDS[2], mean* Sleep disturbance, I: $1.4_{day\ 7}$, $1.3_{day\ 10}$ Somatisation, I: $1.9_{day\ 7}$, $1.6_{day\ 10}$ Anxiety-depression, I: $1.8_{day\ 7}$, $1.7_{day\ 10}$ Apathy, I: $1.8_{day\ 7}$, $1.7_{day\ 10}$ *ZSRS* Change in scores, mean (SD) I: -3.9_{day7}, -8_{day10} (initial score: 70.3)	*HDS[2], mean* Sleep disturbance, C1: $1.5_{day\ 7}$, $1.5_{day\ 10}$ Somatisation, C1: $1.5_{day\ 7}$, $1.5_{day\ 10}$ Anxiety-depression, C1: $1.8_{day\ 7}$, $1.6_{day\ 10}$ Apathy, C1: $2.0_{day\ 7}$, $2.0_{day\ 10}$ *ZSRS* Change in scores, mean (SD) C1: -10.5_{day7}, -10.8_{day10} (initial score: 74.3)	Days 7 & 10 HDS scores NR summarized	?	?	?
Faravelli 1983 Italy	I: 20 C1: 20	0 (1 dropout in I at week 4)	*HRS[2]* Change in scores, mean (SD) I: -11 $(4.2)_{day\ 7}$, -14 $(4.4)_{day\ 14}$ (Initial score: 25)	*HRS[2]* Change in scores, mean (SD) C1: -7 $(6.7)_{day\ 7}$, -11 $(5.6)_{day\ 14}$ (Initial score: 24)	Days 7 & 14 HAM-D_{21} scores/changes estimated from figure SD for change estimated using: sqrt(((n-1)× SDpre2 + (n-1)× SDpost2)/(2n/2))	?	+	?
Hordern 1979 UK	Part I I: 20 C1: 15 Part II: I: 9 C1: 6	Part I I: 5 C1: 3 Part II: I: 1 C1: 2	*HRS[2]* Change in scores, mean (SD) Part I I: -10 $(2.8)_{week\ 1}$, -13 $(2.5)_{week\ 2}$ (Initial score: 32) Part II C1: -8 $(3.8)_{week\ 1}$, -14 $(3.7)_{week\ 2}$ (Initial score: 21)	*HRS[2]* Change in scores, mean (SD) Part I C1: -11 $(2.7)_{week\ 1}$, -13 $(2.9)_{week\ 2}$ (Initial score: 29) Part II C1: -6 $(2.1)_{week\ 1}$, -11 $(2.9)_{week\ 2}$ (Initial score: 17)	Weeks 1 & 2 HRS scores/changes estimated from figure SD for change estimated using: sqrt(((n-1)× SDpre2 + (n-1)× SDpost2)/(2n/2))	?	?	?

* + No or minor problems
? Some problems
- Major problems

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Appendix 4.1
Outcome variable: Depressive/OCD symptoms within 2 weeks

Author Year Country	Patients	Withdrawals - dropouts	Results		Comments	Directness*	Risk of bias*[1]	Precision*
			Intervention	Comparison				
Lecrubier 1980 France	I: 10 C2: 10	0	*HRS*[2] Change in scores, mean (SD) I: -4.35 (1.34) (Initial score: 21.20 (1.45)) Response: ≥50% decrease I: 1/10	*HRS*[2] Change in scores, mean (SD) C2: --9.9 (1.94) (Initial score: 23.25 (2.7)) Response: ≥50% decrease C2: 5/10	Day 5	-	-	-
Pollock 1989 US	I: 11 C1: 11	I: 0 C1: 1/0/0	*HAM-D_{17}*[2] Change in scores, mean (SD) I: -9.8 (3.9)$_{day\ 7}$, -12.9 (6.3)$_{day\ 14}$ (Initial score: 24.9 (3.9)) Response: ≥50% decrease I: 2/11$_{day\ 2}$, 4/11$_{day\ 7}$, 6/11$_{day\ 14}$	*HAM-D_{17}*[2] Change in scores, mean (SD) C1: -11.4 (4.7)$_{day\ 7}$, -13.5 (6.5)$_{day\ 14}$ (Initial score: 22.8 (4.8)) Response: ≥50% decrease I: 1/10$_{day\ 2}$, 6/11$_{day\ 7}$, 8/11$_{day\ 14}$	Day 7 (start of oral treatment) & 14 days Calculated from individual data	?	+/?	-
Sallee 1997 US	I: 8 C3: 8	0	*HAM-D_{21}*[2] Change in scores, mean (SD) I: -15 (4.1) (Initial score: 22.9 (6.0)) Response: ≥50% decrease I: 7/8 *BDI* Change in scores, mean (SD) I: -12.6 (4.6) (Initial score: 20.4 (9.8)) *CGI-S* Change in scores, mean (SD) I: -3.2 (1.0) (Initial score: 5.7 (0.7))	*HAM-D_{21}*[2] Change in scores, mean (SD) C3: -9.0 (6.1) (Initial score: 22.4 (4.0)) Response: ≥50% decrease C3: 3/8 *BDI* Change in scores, mean (SD) C3: -9.4 (4.5) (Initial score: 24.4 (11.2)) *CGI-S* Change in scores, mean (SD) C3: -1.4 (1.1) (Initial score: 5.7 (0.7))	Day 6 Change in HAM-D_{21}[2] scores "differed significantly", P-value NR	-	+	?

* + No or minor problems
? Some problems
- Major problems

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Outcome variable: Depressive/OCD symptoms within 2 weeks

Author Year Country	Patients	Withdrawals - dropouts	Results		Comments	Directness*	Risk of bias*[1]	Precision*
			Intervention	Comparison				
Spreux-Varoquaux 1996 France	I: 13 C1: 14	0	*MADRS* Change in scores, mean (SD) I: -20.6 (15.6) (Initial score: 34.8 (22))	*MADRS* Change in scores, mean (SD) C1: -17.7 (11.4) (Initial score: 32.9 (16))	Day 14 Response ≥50% decrease NR SD for change estimated using: sqrt(((n-1)× SDpre2 + (n-1)× SDpost2)/(2n/2))	?	+/?	?
P2: Patients with OCD								
Fallon 1998 US	I: 29 C3: 25	I: 1 C3: 2	*Y-BOCS* Change in scores, mean (SD) I: -3.4 (6.1) (Initial score: 28.6 (5), $score_{day\ 14}$: 25.2 (7)) *CGI-S* Mean (SD) I: 5.3 (1) (Initial score: 5.9 (1)) Responder (much/very much improved) 6/29	*Y-BOCS* Change in scores, mean (SD) C3: -0.9 (5.0) (Initial score: 27.0 (5), $score_{day\ 14}$: 26.1 (5)) *CGI-S* Mean (SD) C3: 5.7 (5) (Initial score: 5.7 (1)) Responder (much/very much improved) 0/25	Day 14 Mean change NR, calculated, SD for change estimated using sqrt(((n−1) ×SD_{pre}+(n−1) ×SD_{post}) ÷ (2n-2)) Y-BOCS: Response ≥50% decrease NR	?	?	?
Koran 1997 US	I: 7 C1: 8	I: $0_{week\ 1}$, $1_{week\ 2}$ C1: $0_{week\ 1}$, $2_{week\ 2}$	*Y-BOCS* Change in scores, mean (SD) I: -11.0 (5.7)$_{week\ 1}$, -10.2 (9.3)$_{week\ 2}$ (Initial $score_{all}$: 27.7 (7.4)) Response: ≥50% decrease I: $1/6_{week\ 1}$, $1/6_{week\ 2}$ Response: ≥30% decrease	*Y-BOCS* Change in scores, mean (SD) C1: -0.9 (4.2)$_{week\ 1}$, -1.7 (4.2)$_{week\ 2}$ (Initial $score_{all}$: 25.7 (6.3) Response: ≥50% decrease I: $0/6_{week\ 1}$, $1/6_{week2}$ Response: ≥30% decrease	Week 1 (day 4.5 after second pulse-loading dose) & week 2 (after one week of oral clomipramine, following initial pulse loading (2 days) and drug-free period of 4.5 days)	?	?	-

* + No or minor problems
? Some problems
- Major problems

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Appendix 4.1
Outcome variable: Depressive/OCD symptoms within 2 weeks

Author Year Country	Patients	Withdrawals - dropouts	Results		Comments	Directness*	Risk of bias*[1]	Precision*
			Intervention	Comparison				
			I: $4/6_{week\ 1}$, $3/6_{week\ 2}$	I: $0/6_{week\ 1}$, $1/6_{week\ 2}$	Calculated from individual data Two cut-offs for response are provided (Tolin et al., 2005)			
Koran 2006 US	I.: 16 C1: 16	(Initially n=34, 2 dropouts before first outcome ratings, randomisation allocation NR)	*Y-BOCS* Change in scores, mean (SD) I: -2.75 (3.49)	*Y-BOCS* Change in scores, mean (SD) C1: -4.38 (5.44)	Day 6 Y-BOCS absolute scores NR	?	?	?

[1]Assessed using the Cochrane risk-of-bias tool for randomised trials (RoB 2): low risk of bias (+), some concerns (?), or high risk of bias (-)
[2]All Hamilton depression scales are abbreviated HDRS in the main text
BDI = Beck depression, inventory scale, C = comparison, C1 = clomipramine non-parenterally, C2 = other treatment for the condition, C3 = placebo, CGI-S = Clinical global impression severity scale, CI = confidence interval, $HAM\text{-}D_{17}$= Hamilton depression rating scale, 17 items, $HAM\text{-}D_{21}$ = Hamilton depression rating scale, 21 items, $HDRS_{17}$ = Hamilton depression rating scale, first 17 items, HDS = Hamilton depression scale, HRS = Hamilton rating scale, I = intervention, MADRS = Montgomery-Åsberg Depression Rating Scale, NR = not reported, OCD = obsessive-compulsive disorder, P = patients, SD = standard deviation, US = United States, Y-BOCS = Yale-Brown obsessive compulsive scale, ZSRS = Zung self-rating scale

* + No or minor problems
? Some problems
- Major problems

Project: Clomipramine parenterally
Appendix 4.2
Outcome variable: Long-term depressive/OCD symptoms

Author Year Country	Patients	Withdrawals - dropouts	Results		Comments	Directness*	Risk of bias*[1]	Precision *
			Intervention	Comparison				
P1: Patients with depression								
De Cuyper 1981 Belgium	I: 5 C1: 5	0 (HRS) 1 (ZSRS)	*HRS*[2] Change in scores, mean (SD) [improvement in percentage] I: -10.2 (7.0) [27%] Response: ≥50% decrease I: 0/5 *ZSRS* Change in scores, mean (SD) I: -6.8 (2.9)	*HRS*[2] Change in scores, mean (SD) [improvement in percentage] I: -15 (9.7) [49%] Response: ≥50% decrease C1: 2/5 *ZSRS* Change in scores, mean (SD) I: -5.4 (7.1)	Week 4 Initial HRS and ZSRS scores NR Improved scores: numerical change, no cut-off	?	-	-
Escobar 1973 US	I: 14 C1: 17	"dropouts replaced", not further described	*HDS*[2]*, mean* Sleep disturbance, I: 1.4 Somatisation, I: 1.7 Anxiety-depression, I: 1.6 Apathy, I: 1.6 *ZSRS* Change in scores, mean (SD) I: -15.2 (Initial score: 70.3)	*HDS*[2]*, mean* Sleep disturbance, C1: 1.5 Somatisation, C1: 1.7 Anxiety-depression, C1: 1.8 Apathy, C1: 1.9 *ZSRS, mean* Change in scores, mean (SD) C1: -18.1 (Initial score: 74.3)	Day 28 HDS scores NR summarized	?	?	?
Faravelli 1983 Italy	I: 20 C1: 20	0 (1 dropout in I at week 4)	*HRS*[2] Change in scores, mean (SD) I: -17 (5.5) (Initial score: 25)	*HRS*[2] Change in scores, mean (SD) C1: -15 (6.3) (Initial score: 24)	Day 28 HAM-D_{21} scores/changes estimated from figure SD for change estimated using: sqrt(((n-1)× SDpre2 + (n-1)× SDpost2)/(2n/2))	?	+	?

* + No or minor problems
? Some problems
- Major problems

Project: Clomipramine parenterally
Appendix 4.2
Outcome variable: Long-term depressive/OCD symptoms

Author Year Country	Patients	Withdrawals - dropouts	Results		Comments	Directness*	Risk of bias*[1]	Precision *
			Intervention	Comparison				
Fähndrich 1983 Germany	I: 32 C2: 31	I: 2 C2: 1	*HADS*[2] Response: ≥50% decrease I: 20/30	*HADS*[2] Response: ≥50% decrease C2: 21/30	Day 21 HADS scores NR	?	-	?
Hordern 1979 UK	Part I I: 20 C1: 15 Part II: I: 9 C1: 6	Part I I: 5 C1: 3 Part II: I: 1 C1: 2	*HRS*[2] Change in scores, mean (SD) Part I I: -14 (2.8) (Initial score: 32) Part II I: -19 (3.4) (Initial score: 21)	*HRS*[2] Change in scores, mean (SD) Part I C1: -16 (3.0) (Initial score: 29) Part II C1: -14 (3.1) (Initial score: 17)	Week 4 HRS scores/changes estimated from figure SD for change estimated using: sqrt(((n-1)× SDpre2 + (n-1)× SDpost2)/(2n/2))	?	?	?
Lecrubier 1980 France	I: 10 C2: 10	0	*HRS*[2] Change in scores, mean (SD) I: -5.30 (1.72) (Initial score: 21.2 (1.45)) Response: ≥50% decrease I: 4/10	*HRS*[2] Change in scores, mean (SD) C2: -12.9 (2.8) (Initial score: 23.25 (2.7) Response: ≥50% decrease C2: 6/10	Day 15	-	-	-
Pollock 1989 US	I: 11 C1: 11	I: 2 C1: 4	*HAM-D_{17}*[2] Change in scores, mean (SD) I: -14.7 (7.3) (Initial score: 24.8 (4.2)) Response: ≥50% decrease I: 6/9	*HAM-D_{17}*[2] Change in scores, mean (SD) C1: -15.7 (8.0) (Initial score: 21.7 (3.9)) Response: ≥50% decrease I: 5/7	Day 28 Calculated from individual data.	?	+/?	-

* + No or minor problems
? Some problems
- Major problems

Project: Clomipramine parenterally
Appendix 4.2
Outcome variable: Long-term depressive/OCD symptoms

Author Year Country	Patients	Withdrawals - dropouts	Results		Comments	Directness*	Risk of bias*[1]	Precision *
			Intervention	Comparison				
P2: Patients with OCD								
Koran 1997 US	I: 7 C1: 8	I: 1 C1: 2	*Y-BOCS* Change in scores, mean (SD) I: -9.3 (11.4) (Initial score: 27.2 (7.9)) Response: ≥50% decrease I: 2/7 Response: ≥30% decrease I: 4/7	*Y-BOCS* Change in scores, mean (SD) C1: -4.8 (9.8) (Initial score: 26.2 (6.6) Response: ≥50% decrease C1: 0/4 Response: ≥30% decrease C1: 2/4	Week 3 (after two weeks of oral clomipramine, following initial pulse loading (2 days) and drug-free period of 4.5 days) Calculated from individual data Two cut-offs for response are provided (Tolin et al., 2005)	?	?	-
Koran 2006 US	I.: 16 C1: 16	(Initially n=34, 2 dropouts before first outcome ratings, randomisation allocation NR)	*Y-BOCS* Percent change in scores, mean (SD) I: 24 (26)	*Y-BOCS* Percent change in scores, mean (SD) C1: 28 (27)	Week 12 Change in Y-BOCS scores NR Y-BOCS absolute scores NR	?	?	?

[1]Assessed using the Cochrane risk-of-bias tool for randomised trials (RoB 2): low risk of bias (+), some concerns (?), or high risk of bias (-)
[2]All Hamilton depression scales are abbreviated HDRS in the main text
C = comparison, C1: clomipramine non-parenterally, C2: other treatment for the condition, C3: placebo, HADS = Hamilton depression scale, HDRS = Hamilton depression rating scale, HRS = Hamilton rating scale, I = intervention, NR = not reported, OCD = obsessive-compulsive disorder, P = patients, Y-BOCS = Yale-Brown obsessive compulsive scale, ZSRS = Zung self-rating scale

* + No or minor problems
? Some problems
- Major problems

Project: Clomipramine parenterally
Appendix 4.3
Outcome variable: Treatment discontinuation

Author Year Country	Patients	Withdrawals - dropouts	Results		Comments	Directness*	Risk of bias*[1]	Precision *
			Intervention	Comparison				
P1: Patients with depression								
Altamura 2008 Italy	I: 18 C2: 18 C3: 18	NA	I: 0/18	C2: 0/18 C3: 0/18		-	-	-
Faravelli 1983 Italy	I: 20 C1: 20	NA	I: 1/20 (cardiac arrhythmia during infusion)	C1: 0/20		?	+	-
Hordern 1979 UK	Part I I: 20 C1: 15 Part II I: 9 C1: 6	NA	Part I: inpatients I: 5/20 (three failed to improve, one hypotension, one collapse with vomiting after one infusion with an episode of hypotension 5 days later) Part II: outpatients I: 1/9 (rapid deterioration)	Part I: inpatients C1: 3/15 (two hypotension, on suspected jaundice which failed to develop) Part II: outpatients C1: 2/6 (one failed to improve, one had thrombophlebitis)		?	?	?
Pollock 1989 US	I: 11 C1: 11	NA	I: ? (one patient NR, see comment)	C1: 1+? (one because of nervousness; one patient NR, see comment)	One patient discontinued because of extreme anxiety before insertion of the butterfly cannula, randomisation group NR.	?	+/?	-

* + No or minor problems
? Some problems
- Major problems

Project: Clomipramine parenterally
Appendix 4.3
Outcome variable: Treatment discontinuation

Author Year Country	Patients	Withdrawals - dropouts	Results		Comments	Directness*	Risk of bias*[1]	Precision *
			Intervention	Comparison				
P2: Patients with OCD								
Koran 2006 US	I.: 16 C1: 16	(Initially n=34, 2 dropouts before first outcome ratings, randomisation allocation NR)	I: 3/16 (two due to insufficient response, one worsened depression)	C1: 5/16 (one each: consent, contact dermatitis, anxiety and depersonalization, worsened depression, side effects)		?	?	?

[1]Assessed using the Cochrane risk-of-bias tool for randomised trials (RoB 2): low risk of bias (+), some concerns (?), or high risk of bias (-)
C = comparison, C1: clomipramine non-parenterally, C2: other treatment for the condition, C3: placebo, I = intervention, NR = not reported, OCD = obsessive-compulsive disorder, P = patients, UK = United Kingdom, US = United States

* + No or minor problems
? Some problems
- Major problems

Project: Clomipramine parenterally
Appendix 4.4
Outcome variable: Adverse events related to administration via injection/infusion

Author Year Country	Patients	Withdrawals - dropouts	Results		Comments	Directness*	Risk of bias*[1]	Precision *
			Intervention	Comparison				
P1: Patients with depression								
Escobar 1973 US	I: 14 C: 17	"dropouts replaced," not further described	I: 2/14 Treatment withheld due to orthostatic hypotension	C1: 0/17		?	?	-
Faravelli 1983 Italy	I: 20 C1: 20	NA	I: 2/20 (One patient with known heart disease had cardiac arrhythmia during infusion, in week 4. One patient had thrombophlebitis that recovered spontaneously within 2 days)	C1: 0/20		?	+	-
Hordern 1979 UK	Part I I: 20 C1: 15 Part II I: 9 C1: 6	NA	Part I I: 2/20 (Both had hypotension, one of whom collapsed with vomiting and skin pallor at a prior infusion) Part II I: 0/9	Part I C1: 2/15 (Both had hypotension) Part II C1: 1/6 (Thrombophlebitis)		?	?	-
P2: Patients with OCD								
Koran 2006 US	I.: 16 C1: 16	(Initially n=34, 2 dropouts before first outcome ratings, randomisation allocation NR)	I: 2/16 (Treatment withheld due to bradycardia and tachycardia, respectively)	C: 2/16 (Treatment withheld due to bradycardia and hypotension, respectively)		?	?	-

[1]Assessed using the Cochrane risk-of-bias tool for randomised trials (RoB 2): low risk of bias (+), some concerns (?), or high risk of bias (-)
C = comparison, C1: clomipramine non-parenterally, C2: other treatment for the condition, C3: placebo, I = intervention, NA = not applicable, OCD = obsessive-compulsive disorder, P = patients, P1 = patients with depression, P2 = patients with OCD

Project: Clomipramine parenterally

Appendix 5 Aspects regarding directness and study limitations identified during the assessment process contributing to the study being categorised as having no/minor (+), some (?) or major (-) problems.

Author Year Country	Problems contributing to downgrading the study in the assessment					
	Directness[1]		Risk of bias[2]		Precision[1]	
Altamura 2008 Italy	-	Restricted to outpatients, i.e., a subgroup of the P Patients with comorbidity excluded Patients with risk of suicide were excluded Low doses of clomipramine (25 mg) and citalopram (10 mg) No description or flowchart of participant recruitment Characteristics NR	-	Randomisation process: High (randomisation procedure NR, characteristics in randomisation groups NR) Effect of assignment to intervention: High (open-label, responders to SSRI and those dropping out because of side effects excluded) Missing outcome data: Low Outcome measurement: Some concerns (open-label, blinded raters) Selection of reported results: Low	?	Small study sample Power calculations not provided (Treatment discontinuation: no events, i.e. major problems)
De Cuyper 1981 Belgium	?	Restricted to outpatients, recently hospitalised, mean HDRS: 32 (20–43) 3/10 were bipolar without mood stabilisers No description or flowchart of participant recruitment	-	Randomisation process: High (randomisation procedure NR, older ages in C, 1 vs 2 patients with bipolar disorder) Effect of assignment to intervention: High (open-label) Missing outcome data: Low Outcome measurement: High (Not blinded) Selection of reported results: Low	-	Small study sample Power calculations not provided PK focus
Drago 1983 Italy	?	C: maprotiline (not used today) No description or flowchart of participant recruitment	+/?	Randomisation process: Some concerns (randomisation procedure NR, duration of symptoms: 220 vs. 157 days) Effect of assignment to intervention: Low Missing outcome data: Low Outcome measurement: Low Selection of reported results: Low	?	Small study sample Power calculations not provided
Escobar 1973 US	?	No description or flowchart of participant recruitment	?	Randomisation process: Some concerns (randomisation procedure NR, characteristics in randomisation groups not explicitly presented, reportedly 8/14 vs	?	Small study sample Power calculations not provided (Adverse events: two events, i.e. major problems)

Project: Clomipramine parenterally

Appendix 5 Aspects regarding directness and study limitations identified during the assessment process contributing to the study being categorised as having no/minor (+), some (?) or major (-) problems.

Author Year Country	Problems contributing to downgrading the study in the assessment					
	Directness[1]		Risk of bias[2]		Precision[1]	
				4/17 had reactive depression, C "had slightly higher pathology scores") Effect of assignment to intervention: Low Missing outcome data: Some concerns (dropouts replaced) Outcome measurement: Low Selection of reported results: Low		
Fallon 1998 US	?	P: no/partial response to clomipramine PO, or inadequate trial because of side effects No description or flowchart of participant recruitment	?	Randomisation process: Low Effect of assignment to intervention: Some concerns (all patients were treatment refractory to oral clomipramine) Missing outcome data: Low Outcome measurement: Low Selection of reported results: Low	?	Power calculations not provided
Faravelli 1983 Italy	?	No description or flowchart of participant recruitment	+	Randomisation process: Some concerns (randomisation procedure NR) Effect of assignment to intervention: Low Missing outcome data: Low Outcome measurement: Low Selection of reported results: Low	?	Small study sample Power calculations not provided (Treatment discontinuation: one event, i.e. major problems. Adverse events: two events, i.e. major problems)
Fähndrich 1983 Germany	?	Preceded by sleep deprivation C: maprotiline (not used today) No description or flowchart of participant recruitment	-	Randomisation process: Some concerns (randomisation procedure NR) Effect of assignment to intervention: Some concerns (open-label but both groups received active treatment) Missing outcome data: Low Outcome measurement: High (open-label, assessments NR) Selection of reported results: Low	?	Power calculations not provided

Project: Clomipramine parenterally

Appendix 5 Aspects regarding directness and study limitations identified during the assessment process contributing to the study being categorised as having no/minor (+), some (?) or major (-) problems.

Author Year Country	Problems contributing to downgrading the study in the assessment					
	Directness[1]		**Risk of bias[2]**		**Precision[1]**	
Hordern 1979 UK	?	Restricted to those who had not received ECT within three months and antidepressant drugs within two weeks No description or flowchart of participant recruitment	?	Randomisation process: Some concerns (randomisation procedure NR, only age and sex reported in comparison groups) Effect of assignment to intervention: Low Missing outcome data: Some concerns (8/35 dropped out in part I (6 vs. 2), 3/15 in part II (1 vs. 2)) Outcome measurement: Low Selection of reported results: Low	?	Small study sample Power calculations not provided (Adverse events: five events, i.e. major problems)
Koran 1997 US	?	No description or flowchart of participant recruitment	?	Randomisation process: Some concerns (randomisation procedure NR) Effect of assignment to intervention: Low Missing outcome data: Some concerns (reasons for dropouts NR) Outcome measurement: Low Selection of reported results: Low	-	Very small study sample Power calculations not provided
Koran 2006 US	?	No flowchart of participant recruitment Restricted to patients who had failed to benefit from two oral SRIs	?	Randomisation process: Some concerns (characteristics in comparison groups only described as “no significant differences”, apart from age at onset: 18.7 vs. 13.1 years) Effect of assignment to intervention: Some concerns (14/32 had not responded to clomipramine PO) Missing outcome data: Low Outcome measurement: Low Selection of reported results: Low	?	Posthoc power calculation: 60% to detect an effect size of 0.7 (Adverse events: four events, i.e. major problems)
Lecrubier 1980 France	-	C: salbutamol (not used) No description or flowchart of participant recruitment	-	Randomisation process: Some concerns (used Taves procedures to allow equilibration, HRS score at baseline: 21.20 vs. 23.25, 3 vs. 6 patients had previous response to tricyclics treatment)	-	Very small study sample Power calculations not provided

Project: Clomipramine parenterally

Appendix 5 Aspects regarding directness and study limitations identified during the assessment process contributing to the study being categorised as having no/minor (+), some (?) or major (-) problems.

Author Year Country	Problems contributing to downgrading the study in the assessment					
	Directness[1]		Risk of bias[2]		Precision[1]	
				Effect of assignment to intervention: High (open-label) Missing outcome data: Low Outcome measurement: Some concerns (open-label, blinded raters) Selection of reported results: Low		
Pollock 1989 US	?	No description or flowchart of participant recruitment	+/?	Randomisation process: Some concerns (randomisation procedure NR, 34 vs. 42 years) Effect of assignment to intervention: Low Missing outcome data: Low Outcome measurement: Low Selection of reported results: Low	-	Very small study sample Power calculations not provided
Sallee 1997 US	-	No description or flowchart of participant recruitment Restricted to adolescents, clomipramine PO not recommended to this age group according to Pharmaceutical Specialities in Sweden Patients with risk of suicide were excluded Restricted to patients with initial 4-week washout for antidepressant (6 weeks for fluoxetine)	+	Randomisation process: Low Effect of assignment to intervention: Low Missing outcome data: Low Outcome measurement: Low Selection of reported results: Low	?	Small study sample Power calculations not provided
Spreux-Varoquaux 1996 France	?	P: No SSRI for 3 months required No description or flowchart of participant recruitment	+/?	Randomisation process: Some concerns (randomisation procedure NR, 50 vs. 39 years) Effect of assignment to intervention: Low Missing outcome data: Low Outcome measurement: Low Selection of reported results: Low	?	Small study sample Power calculations not provided Focus: plasma serotonin

Project: Clomipramine parenterally

Appendix 5 Aspects regarding directness and study limitations identified during the assessment process contributing to the study being categorised as having no/minor (+), some (?) or major (-) problems.

Author Year Country	Problems contributing to downgrading the study in the assessment		
	Directness[1]	Risk of bias[2]	Precision[1]

C = comparison, ECT = electroconvulsive treatment, EEG = electroencephalogram, HDRS = Hamilton depression rating scale, HRS = Hamilton rating scale, NR = not reported, PK = pharmacokinetics, PO = per os, SRI = serotonin reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, Y-BOCS = Yale-Brown obsessive compulsive scale,

[1]Assessed using the checklist developed by HTA-centrum: no/minor (+), some (?), or major (-) problems

[2]Assessed using the Cochrane risk-of-bias tool for randomised trials (RoB 2): low risk of bias (+), some concerns (?), or high risk of bias (-)

Appendix 6 Questionnaire regarding the use of parenteral clomipramine in Swedish psychiatric clinics.

Question	Response options
1. Which psychiatric clinic do you work at?	Single line text
2. Which region?	Single line text
3. Has your clinic used clomipramine infusion as a treatment method during the past 3 (THREE) years?	• Yes • No
4. If yes, how often is clomipramine infusion used at your clinic?	Single choice (required) • 1–2 times per year • 3–6 times per year • 6–12 times per year • More than 12 times per year • Not applicable (0 times per year)
5. Is clomipramine infusion considered an alternative to ECT at your clinic?	• Yes, always • Yes, in certain cases • No, never • Uncertain
6. For which conditions do you primarily use clomipramine infusion? (Multiple answers possible)	Multiple choice • Moderate to severe depression • Treatment-resistant depression • Obsessive-compulsive disorder • Psychotic depression • Anxiety disorders • Other