PICO 1

**Population**

Adult patients over the age of 18 (both outpatient and inpatient) with a difficult to treat depression (DTD) of moderate to severe degree of severity, diagnosed according to ICD-10 or DSM-IV or DSM-5 criteria. By DTD is meant patients who have not responded to different types of antidepressants given in a sufficient dose and for a sufficiently long time (≥4 weeks), or have had depression for over two years regardless of treatment, or are assessed treatment-resistant on an assessment scale to treatment-resistant depression (e.g. Maudsley). If dysthymia or bipolar exceeds 10% of the population, it will result in a downgrade in GRADE.

**Intervention**

Repetitive transcranial magnetic stimulation (rTMS), incl. high-frequency rTMS given to the left dorsolateral prefrontal cortex (DLPFC) or low-frequency rTMS given to the right DLPFC. Treatment must consist of a series of a minimum of 10 daily stimulations (excluding weekends), corresponding to treatment time of at least 2 weeks.

**Comparison**

The included studies should compare the effect of rTMS with no concomitant new intervention (i.e. no active comparator).

This includes studies where:

- rTMS as a supplement to treatment as usual (TAU) is compared with TAU alone;

- rTMS is compared with no treatment;

The absence of rTMS in these studies may or may not be disguised by placebo administration (sham rTMS). TAU consists of what else might be given, and which is often outside the sphere of control of the experiments.

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| **Outcome** | **Timeframe** | **Critical/important** |
| Remission (≤7 in HDRS-17, ≤9 in HDRS-21, ≤4 in HDRS-6, ≤11 in MADRS, ≤6 in MAS) | After ended treatment | Critical |
| Level of function (e.g., Short-Form 36, SDS, PSP), GAF-S, GAF-F, SOFAS) | After ended treatment | Critical |
| Symptoms of depression (e.g., HDRS-17, HAM-D-6, BDI, MADRS, MES) | After ended treatment | Important |
| Response (≥50% reduction in HDRS-17 or HDRS-6 or MADRS or MAS) | After ended treatment | Important |
| Symptoms of depression (e.g., HDRS-17, HAM-D-6, BDI, MADRS, MES) | longest follow up (min. 6 months.) | Important |
| Quality of life (e.g. WHO-5, WHOQOL-BREF, QLDS) | After ended treatment | Important |
| Remission (≤7 in HDRS-17, ≤9 in HDRS-21, ≤4 in HDRS-6, ≤11 in MADRS, ≤6 in MAS) | Longest follow up (min. 6 months.) | Important |
| Adverse events - admission | After ended treatment | Critical |
| Adverse events – suicide attempt | After ended treatment | Critical |
| Additional side effects | After ended treatment | Important |
| Defection/All-cause discontinuation | After ended treatment | Important |

**PICO 2**

**Population**

Adult patients over the age of 18 (both outpatient and inpatient) with a difficult to treat depression (DTD) of moderate to severe degree of severity, diagnosed according to ICD-10 or DSM-IV or DSM-5 criteria. By DTD is meant patients who have not responded to different types of antidepressants given in a sufficient dose and for a sufficiently long time (≥4 weeks), or have had depression for over two years regardless of treatment, or are assessed treatment-resistant on an assessment scale to treatment-resistant depression (e.g. Maudsley). If dysthymia or bipolar exceeds 10% of the population, it will result in a downgrade in GRADE.

**Intervention**

Minimum one administration of ketamine/esketamine in subanesthetic doses given intravenously, intranasally, or orally.

**Comparison**

The included studies should compare the effect of ketamine/esketamine with no concomitant new intervention (i.e. no active comparator).

This includes studies where:

- ketamine / esketamine as a supplement to treatment as usual (TAU) is compared with TAU alone;

- ketamine / esketamine is compared with no treatment;

The absence of ketamine/esketamine in these studies may or may not be disguised by placebo administration. TAU consists of what else might be given, and which is often outside the sphere of control of the experiments.

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| **Outcome** | **Timeframe** | **Critical/important** |
| Remission (≤7 in HDRS-17, ≤9 in HDRS-21, ≤4 in HDRS-6, ≤11 in MADRS, ≤6 in MAS) | After ended treatment | Critical |
| Level of function (e.g., Short-Form 36, SDS, PSP), GAF-S, GAF-F, SOFAS) | After ended treatment | Critical |
| Symptoms of depression (e.g., HDRS-17, HAM-D-6, BDI, MADRS, MES) | After ended treatment | Important |
| Response (≥50% reduction in HDRS-17 or HDRS-6 or MADRS or MAS) | After ended treatment | Important |
| Symptoms of depression (e.g., HDRS-17, HAM-D-6, BDI, MADRS, MES) | Longest follow up (min. 6 months.) | Important |
| Quality of life (e.g., WHO-5, WHOQOL-BREF, QLDS) | After ended treatment | Important |
| Remission (≤7 in HDRS-17, ≤9 in HDRS-21, ≤4 in HDRS-6, ≤11 in MADRS, ≤6 in MAS) | longest follow up (min. 6 months.) | Important |
| Adverse events - admission | After ended treatment | Critical |
| Adverse events – suicide attempt | After ended treatment | Critical |
| Abuse of ketamine/esketamin | After ended treatment | Important |
| Additional side effects | After ended treatment | Important |
| Defection/All-cause discontinuation | After ended treatment | Important |

**PICO 3**

**Population**

Adult patients over the age of 18 (both outpatient and inpatient) with a difficult to treat depression (DTD) of moderate to severe degree of severity, diagnosed according to ICD-10 or DSM-IV or DSM-5 criteria. By DTD is meant patients who have not responded to different types of antidepressants given in a sufficient dose and for a sufficiently long time (≥4 weeks), or have had depression for over two years regardless of treatment, or are assessed treatment-resistant on an assessment scale to treatment-resistant depression (e.g. Maudsley). If dysthymia or bipolar exceeds 10% of the population, it will result in a downgrade in GRADE.

**Intervention**

Light treatment with clear white light (> 5,000 lux), administered daily> 30 minutes for a minimum of 2 weeks.

**Comparison**

The included studies should compare the effect of light therapy with no concomitant new intervention (i.e. no active comparator). This means studies where:

- light treatment as a supplement to treatment as usual (TAU) is compared with TAU alone;

- light treatment is compared with no treatment;

The absence of light therapy in these studies may or may not be disguised by the administration of placebo (e.g. dim light). TAU consists of what else might give, and which is often outside the control sphere of the experiments.

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| **Outcome** | **Timeframe** | **Critical/important** |
| Remission (≤7 in HDRS-17, ≤9 in HDRS-21, ≤4 in HDRS-6, ≤11 in MADRS, ≤6 in MAS) | After ended treatment | Critical |
| Level of function (e.g., Short-Form 36, SDS, PSP), GAF-S, GAF-F, SOFAS) | After ended treatment | Critical |
| Symptoms of depression (e.g., HDRS-17, HAM-D-6, BDI, MADRS, MES) | After ended treatment | Important |
| Response (≥50% reduction in HDRS-17 or HDRS-6 or MADRS or MAS) | After ended treatment | Important |
| Symptoms of depression (e.g. HDRS-17, HAM-D-6, BDI, MADRS, MES) | longest follow up (min. 6 months.) | Important |
| Quality of life (e.g. WHO-5, WHOQOL-BREF, QLDS) | After ended treatment | Important |
| Remission (≤7 in HDRS-17, ≤9 in HDRS-21, ≤4 in HDRS-6, ≤11 in MADRS, ≤6 in MAS) | longest follow up (min. 6 months.) | Important |
| Adverse events - admission | After ended treatment | Critical |
| Adverse events – suicide attempt | After ended treatment | Critical |
| Additional side effects | After ended treatment | Important |
| Defection/All-cause discontinuation | After ended treatment | Important |

**PICO 4**

**Population**

Adult patients over the age of 18 (both outpatient and inpatient) with a difficult to treat depression (DTD) of moderate to severe degree of severity, diagnosed according to ICD-10 or DSM-IV or DSM-5 criteria. By DTD is meant patients who have not responded to different types of antidepressants given in a sufficient dose and for a sufficiently long time (≥4 weeks), or have had depression for over two years regardless of treatment, or are assessed treatment-resistant on an assessment scale to treatment-resistant depression (e.g. Maudsley). If dysthymia or bipolar exceeds 10% of the population, it will result in a downgrade in GRADE.

**Intervention**

Intervention is manual CBASP minimum of 12 sessions.

**Comparison**

The included studies should compare the effect of CBASP with no concomitant new intervention (ie no active comparator).

This includes studies where:

- CBASP as a supplement to treatment as usual (TAU) is compared with TAU alone;

- CBASP is compared with no treatment;

TAU consists of what else might be given, and which is often outside the sphere of control of the experiments.

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| **Outcome** | **Timeframe** | **Critical/important** |
| Remission (≤7 in HDRS-17, ≤9 in HDRS-21, ≤4 in HDRS-6, ≤11 in MADRS, ≤6 in MAS) | After ended treatment | Critical |
| Level of function (e.g., Short-Form 36, SDS, PSP), GAF-S, GAF-F, SOFAS) | After ended treatment | Critical |
| Symptoms of depression (e.g., HDRS-17, HAM-D-6, BDI, MADRS, MES) | After ended treatment | Important |
| Response (≥50% reduction in HDRS-17 or HDRS-6 or MADRS or MAS) | After ended treatment | Important |
| Symptoms of depression (e.g. HDRS-17, HAM-D-6, BDI, MADRS, MES) | longest follow up (min. 6 months.) | Important |
| Quality of life (e.g. WHO-5, WHOQOL-BREF, QLDS) | After ended treatment | Important |
| Remission (≤7 in HDRS-17, ≤9 in HDRS-21, ≤4 in HDRS-6, ≤11 in MADRS, ≤6 in MAS) | Longest follow up (min. 6 months.) | Important |
| Adverse events - admission | After ended treatment | Critical |
| Adverse events – suicide attempt | After ended treatment | Critical |
| Additional side effects | After ended treatment | Important |
| Defection/All-cause discontinuation | After ended treatment | Important |

**PICO 5**

**Population**

Adult patients over the age of 18 (both outpatient and inpatient) with a difficult to treat depression (DTD) of moderate to severe degree of severity, diagnosed according to ICD-10 or DSM-IV or DSM-5 criteria. By DTD is meant patients who have not responded to different types of antidepressants given in a sufficient dose and for a sufficiently long time (≥4 weeks), or have had depression for over two years regardless of treatment, or are assessed treatment-resistant on an assessment scale to treatment-resistant depression (e.g. Maudsley). If dysthymia or bipolar exceeds 10% of the population, it will result in a downgrade in GRADE.

**Intervention**

Intervention is manual psychotherapeutic treatment, that describes being specifically targeted repetitive negative thinking, including ruminations (treatment must be at least 12 sessions). The following types of treatment are included (Meta-Cognitive Therapy (MCT), Rumination-focused Cognitive Behavioral Therapy (rf-CBT, Concreteness Training (CNT), Mindfulness-based Cognitive Behavioral Therapy (MBCT), Cognitive Control Training (CCT), Attention Bias Modification (ABM), Cognitive Bias Modification (CBM)).

**Comparison**

The included studies should compare the effect of rumination-targeted psychotherapy with no concomitant new intervention (i.e. no active comparator). This includes studies where:

- psychotherapy targeted rumination as a supplement to treatment as usual (TAU) is compared with TAU alone;

- psychotherapy targeted rumination is compared with no treatment;

TAU consists of what else might be given, and which is often outside the sphere of control of the experiments.

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| **Outcome** | **Timeframe** | **Critical/important** |
| Remission (≤7 in HDRS-17, ≤9 in HDRS-21, ≤4 in HDRS-6, ≤11 in MADRS, ≤6 in MAS) | After ended treatment | Critical |
| Level of function (e.g., Short-Form 36, SDS, PSP), GAF-S, GAF-F, SOFAS) | After ended treatment | Critical |
| Symptoms of depression (e.g., HDRS-17, HAM-D-6, BDI, MADRS, MES) | After ended treatment | Important |
| Response (≥50% reduction in HDRS-17 or HDRS-6 or MADRS or MAS) | After ended treatment | Important |
| Symptoms of depression (e.g., HDRS-17, HAM-D-6, BDI, MADRS, MES) | longest follow up (min. 6 months.) | Important |
| Quality of life (e.g., WHO-5, WHOQOL-BREF, QLDS) | After ended treatment | Important |
| Remission (≤7 in HDRS-17, ≤9 in HDRS-21, ≤4 in HDRS-6, ≤11 in MADRS, ≤6 in MAS) | Longest follow up (min. 6 months.) | Important |
| Adverse events - admission | After ended treatment | Critical |
| Adverse events – suicide attempt | After ended treatment | Critical |
| Additional side effects | After ended treatment | Important |
| Defection/All-cause discontinuation | After ended treatment | Important |

**PICO 6**

**Population**

Adult patients over the age of 18 (both outpatient and inpatient) with a difficult to treat depression (DTD) of moderate to severe degree of severity, diagnosed according to ICD-10 or DSM-IV or DSM-5 criteria. By DTD is meant patients who have not responded to different types of antidepressants given in a sufficient dose and for a sufficiently long time (≥4 weeks), or have had depression for over two years regardless of treatment, or are assessed treatment-resistant on an assessment scale to treatment-resistant depression (e.g. Maudsley). If dysthymia or bipolar exceeds 10% of the population, it will result in a downgrade in GRADE.

**Intervention**

Cognitive remediation is understood as a structured program aimed at improving cognition. The minimum requirement for the intervention is 1 x 2 hours per week for 6 weeks.

**Comparison**

The included studies should compare the effect of cognitive remediation with no concomitant new intervention (i.e. no active comparator).

This includes studies where:

- cognitive remediation as a supplement to treatment as usual (TAU) is compared with TAU alone;

- cognitive remediation is compared with no treatment;

TAU consists of what else might be given, and which is often outside the sphere of control of the experiments.

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| **Outcome** | **Timeframe** | **Critical/important** |
| Remission (≤7 in HDRS-17, ≤9 in HDRS-21, ≤4 in HDRS-6, ≤11 in MADRS, ≤6 in MAS) | After ended treatment | Critical |
| Level of function (e.g., Short-Form 36, SDS, PSP), GAF-S, GAF-F, SOFAS) | After ended treatment | Critical |
| Symptoms of depression (e.g., HDRS-17, HAM-D-6, BDI, MADRS, MES) | After ended treatment | Important |
| Response (≥50% reduction in HDRS-17 or HDRS-6 or MADRS or MAS) | After ended treatment | Important |
| Symptoms of depression (e.g., HDRS-17, HAM-D-6, BDI, MADRS, MES) | longest follow up (min 6 months.) | Important |
| Quality of life (e.g., WHO-5, WHOQOL-BREF, QLDS) | After ended treatment | Important |
| Remission (≤7 in HDRS-17, ≤9 in HDRS-21, ≤4 in HDRS-6, ≤11 in MADRS, ≤6 in MAS) | Longest follow up (min 6 months.) | Important |
| Adverse events - admission | After ended treatment | Critical |
| Adverse events – suicide attempt | After ended treatment | Critical |
| Additional side effects | After ended treatment | Important |
| Defection/All-cause discontinuation | After ended treatment | Important |