Review protocol for review question: What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode?

Table 69: Review protocol

Field (based on PRISMA-P)	Content
Review question	What are the relative benefits and harms of further-line psychological, psychosocial, pharmacological and physical interventions (alone or in combination), for adults with depression showing an inadequate response to at least one previous intervention for the current episode?
Type of review question	Intervention review
Objective of the review	To identify the most effective interventions for people who have had no or limited response to previous treatment(s) (for the current episode), have not tolerated previous treatment(s) (for the current episode), or have treatment-resistant depression
Population	• Adults in a depressive episode whose depression has not responded or there has been limited response to previous treatment(s) (for the current episode) according to DSM, ICD or similar criteria, or (residual) depressive symptoms as indicated by depression scale score, or who have not tolerated previous treatment (for the current episode), or who are defined as meeting criteria for treatment-resistant depression, and who have been randomised to the further-line interventions at the point at which they had no/inadequate/limited response If some, but not all, of a study's participants are eligible for the review, then we will include a study if at least 80% of its participants are eligible for this review.
Exclude	• Trials of women with antenatal or postnatal depression • Trials of children and young people (mean age under 18 years) • Trials of people with learning disabilities • Trials of people with bipolar disorder • Trials of adults in contact with the criminal justice system (not solely as a result of being a witness or victim) • Trials that specifically recruit participants with a physical health condition in addition to depression (e.g. depression in people with diabetes)
Intervention	Interventions listed below are examples of interventions which may be included either alone or in combination:

Field (based on PRISMA-P)	Content
	Psychological interventions • Behavioural therapies (including behavioural activation, behavioural therapy [Lewinsohn 1976], coping with depression group) • Cognitive and cognitive behavioural therapies (including CBT individual or group, problem solving, rational emotive behaviour therapy [REBT], third-wave cognitive therapies, Mindfulness-based Cognitive Therapy [MBCT] and Cognitive Behavioural Analysis System of Psychotherapy [CBASP]) • Counselling (including emotion-focused therapy [EFT], non-directive/supportive/ person-centred counselling and relational client-centred therapy) • Interpersonal psychotherapy (IPT) • Psychodynamic psychotherapies (including short-term psychodynamic psychotherapy, long-term psychodynamic psychotherapy and psychodynamic counselling) • Psychoeducational interventions (including psychoeducational group programmes) • Self-help with or without support (including cognitive bibliotherapy with or without support, computerised CBT [CCBT] with or without support, computerised psychodynamic therapy with or without support) • Art therapy • Music therapy • Eye movement desensitization and reprocessing (EMDR) (for depression, not PTSD) **Psychosocial interventions:** • Peer support (including befriending, mentoring, and community navigators) • Mindfulness, meditation or relaxation (including mindfulness-based stress reduction [MBSR]) **Pharmacological interventions** Antidepressants SSRIs • Citalopram • Escitalopram • Fluvoxamine • Fluoxetine • Paroxetine • Sertraline TCAs

Field (based on PRISMA-P)	Content
	• Amineptine[1] • Amitriptyline • Clomipramine • Desipramine[2] • Imipramine • Lofepramine • Nortriptyline TeCAs • Mianserin SNRIs • Duloxetine • Venlafaxine Other antidepressant drugs • Bupropion[3] • Mirtazepine Anticonvulsants • Lamotrigine[3] Antipsychotics • Amisulpride[3] • Aripiprazole[3] • Olanzapine[3] • Quetiapine • Risperidone[3] • Ziprasidone[2] Anxiolytics • Buspirone

Field (based on PRISMA-P)	Content
	Stimulants • Methylphenidate[3] Other agents • Lithium • Omega-3 fatty acids • Thyroid hormone[3] **Physical interventions** • Acupuncture • ECT • Exercise • Yoga • Light therapy (for depression, not SAD) Interventions will be categorised into the following strategies: • Dose escalation strategies • Switching strategies (including switching to another antidepressant of the same class, switching to another antidepressant of a different class, and switching to a non-antidepressant treatment) • Augmentation strategies (including augmenting the antidepressant with another antidepressant, augmenting the antidepressant with a non-antidepressant agent and augmenting the antidepressant with a psychological/psychosocial/physical intervention)
Comparison	• Other active intervention (must also meet inclusion criteria above) • Treatment as usual • Waitlist • No treatment • Placebo In addition to placebo and head-to-head comparators, comparator treatment strategies include: • Continuing with the antidepressant at the same dose • Continuing with the antidepressant-only
Outcomes	**Critical outcomes:**

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	Efficacy • Depression symptomatology (mean endpoint score or change in depression score from baseline) • Remission (usually defined as a cut off on a depression scale) • Response (usually defined as at least 50% improvement from the baseline score on a depression scale) The following depression scales will be included in the following hierarchy: • MADRS • HAMD • QIDS • PHQ • CGI (for dichotomous outcomes only) • CES-D • BDI • HADS-D (depression subscale) • HADS (full scale) Acceptability/tolerability • Discontinuation due to any reason (including side effects) • Discontinuation due to side effects (for pharmacological trials) **Important outcomes:** • Quality of life: ○ Quality of life (as assessed with a validated scale, including the 12-item/36-item Short-Form Survey [SF-12/SF-36], 26-item short version of the World Health Organization Quality of Life assessment [WHOQOL-BREF], EuroQoL [EQ5D], Quality of Life Depression Scale [QLDS], Quality of Life Enjoyment and Satisfaction Questionnaire [Q-LES-Q], Quality of Life Inventory [QoLI], and World Health Organization 5-item Well-Being Index [WHO-5]) • Personal, social, and occupational functioning: ○ Global functioning (as assessed with a validated scale, including Global Assessment of Functioning [GAF], Global Assessment Scale [GAS], and Social and Occupational Functioning Assessment Scale [SOFAS]) ○ Functional impairment (as assessed with a validated scale, including Sheehan Disability Scale [SDS], Social Adjustment Scale [SAS], and Work and Social Adjustment Scale [WSAS])

Field (based on PRISMA-P)	Content
	○ Sleeping difficulties (as assessed with a validated scale, including Insomnia Severity Index [ISI] and Pittsburgh Sleep Quality Index [PSQI]) ○ Employment (for instance, % unemployed) ○ Interpersonal problems (as assessed with a validated scale, including Inventory of Interpersonal Problems [IIP]) Outcomes will be assessed at endpoint and follow-up (data for all available follow-up periods of at least 1-month post-intervention will be extracted and will be grouped into categories for analysis, for instance, 1-3 months, 4-6 months, 7-9 months, 10-12 months, 13-18 months, 19-24 months, and >2 years).
Study design	RCTs Systematic reviews of RCTs
Include unpublished data?	Conference abstracts, dissertations and unpublished data will not be included unless the data can be extracted from elsewhere (for instance, from the previous guideline).
Restriction by date?	All relevant studies from existing reviews from the 2009 guideline and from previous searches (pre-2016) will be carried forward. No restriction on date for the updated search, studies published between database inception and the date the searches are run will be sought.
Minimum sample size	N = 10 in each arm Studies with <50% completion data (drop out of >50%) will be excluded.
Study setting	Primary, secondary, tertiary and social care settings Non-English-language papers will be excluded (unless data can be obtained from an existing review).
The review strategy	**Data Extraction (selection and coding)** Citations from each search will be downloaded into EndNote and duplicates removed. Titles and abstracts of identified studies will be screened by two reviewers for inclusion against criteria, until a good inter-rater reliability has been observed (percentage agreement =>90%). Initially 10% of references will be double-screened. If inter-rater agreement is good then the remaining references will be screened by one reviewer. All primary-level studies included after the first scan of citations will be acquired in full and re-evaluated for eligibility at the time they are being entered into a study database (standardised template created in Microsoft Excel). At least 10% of data extraction will be double-coded. Discrepancies or difficulties with coding will be resolved through discussion between reviewers or the opinion of a third reviewer will be sought. **Data Analysis** A meta-analysis using a random-effects model will be conducted to combine results from similar studies. An intention to treat (ITT) approach will be taken where possible.

Field (based on PRISMA-P)	Content
	Risk of bias will be assessed at the study level using the Cochrane risk of bias tool. This assessment includes: adequacy of randomisation (sufficient description of randomisation method, allocation concealment and any baseline difference between groups); blinding (of participants, intervention administrators and outcome assessors); attrition ('at risk of attrition bias' defined as a dropout of more than 20% and completer analysis used, or a difference of >20% between the groups); selective reporting bias (is the protocol registered, are all outcomes reported); other bias (for instance, conflict of interest in funding). Risk of bias will also be assessed at the outcome level using GRADE. For heterogeneity, outcomes will be downgraded once if I2>50%, twice if I2 >80%. For imprecision, outcomes will be downgraded using rules of thumb. If the 95% CI is imprecise i.e. crosses the line of no effect and the threshold for clinical benefit/harm, 0.8 or 1.25 (dichotomous) or -0.5 or 0.5 SMD (for continuous), the outcome will be downgraded. Outcomes will be downgraded one or two levels depending on how many lines it crosses. If the 95% CI is not imprecise, we will consider whether the criterion for Optimal Information Size is met (for dichotomous outcomes, 300 events; for continuous outcomes, 400 participants), if not we will downgrade one level.
Heterogeneity (sensitivity analysis and subgroups)	Where possible, the following subgroup analyses will be considered: • Psychotic depression • Depression with coexisting personality disorder • Chronic depression
Data management (software)	Endnote was used to sift through the references identified by the search, and for data extraction Pairwise meta-analyses and production of forest plots was done using Cochrane Review Manager (RevMan5). 'GRADEpro' was used to assess the quality of evidence for each outcome.
Notes	If trials specifically recruited populations with chronic depressive symptoms they would be included in this review (as opposed to RQ 2.6) if the treatment was further-line and if they reported a critical outcome. A Cochrane review of psychological therapies for treatment-resistant depression in adults was identified (Ijaz et al., 2018) which was used a source of studies for the review of psychological interventions. 1. Amineptine is not available to prescribe as a medicine (although it falls under Class C of the Misuse of Drugs Act 1971, and listed as Schedule 2 under the Controlled Drugs Regulations 2001). However, this drug is included in this review in order to assess the class effect of pharmacological interventions for depression 2. Desipramine and ziprasidone are not available in the UK to prescribe. However, these drugs are included in this review in order to assess the class effect of pharmacological interventions for depression

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	3. None of these drugs are licensed for use in depression. However, they are included in the review in order to assess harms and efficacy for off-label use and to assess the class effect of pharmacological interventions for depression
Information sources – databases and dates	Database(s): Embase 1974 to Present, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; Cochrane Library; WEB OF SCIENCE
Identify if an update	Update of CG90 (2009)
Author contacts	For details please see the guideline in development web site.
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual 2014
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual 2014. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/.
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual 2014
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods chapter.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual 2014.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Alliance (NGA) and chaired by Dr Navneet Kapur in line with section 3 of Developing NICE guidelines: the manual 2014. Staff from the NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter.

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Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds NGA to develop guidelines for those working in the NHS, public health and social care in England
PROSPERO registration number	CRD42019151342

BDI: Beck depression inventory;(C)CBT: (computerised) cognitive behavioural therapy; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CES-D: Centre of epidemiology studies – depression; CGI: clinical global impressions; CI: confidence interval; DARE: Database of Abstracts of Reviews of Effects; DSM: Diagnostic and statistical manual; ECT: electroconvulsive therapy; EFT: emotion-focused therapy; EMDR: eye movement desensitization and reprocessing; EQ-5D: European quality of life 5 dimensions; GAF: global assessment of functioning; GAS: global assessment scale; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HADS-D: hospital anxiety and depression scale – depression; HAMD: Hamilton Depression Rating Scale; ICD: International classification of diseases; IIP: inventory of interpersonal problems; ISI: insomnia severity index; ITT: intention to treat; MADRS: Montgomery–Åsberg Depression Rating Scale; MBSR: Mindfulness-based stress reduction; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; PHQ-9: patient health questionnaire-9; PSQI: Pittsburgh sleep quality index; PTSD: post-traumatic stress disorder; QIDS: quick inventory of depressive symptomatology; QLDS: quality of life depression scale; Q-LES-Q: quality of life enjoyment and satisfaction questionnaire QOLI: quality of life inventory RCT: randomised controlled trial; REBT: rational emotive behaviour therapy; RoB: risk of bias; SAD: seasonal affective disorder; SAS: social adjustment scale; SDS: Sheehan disability scale; SMD: standardised mean difference; SNRI: serotonin-noradrenaline reuptake inhibitor; SOFAS: social and occupational functioning assessment scale; SSRI: selective serotonin reuptake inhibitor; TAU: treatment as usual; TCA: tricyclic antidepressant; TeCA: tetracyclic antidepressant; WHOQOL-BRIEF: World health organization quality of life assessment (brief); WHO-5: world health organization 5-item wellbeing index; WSAS: work and social adjustment scale