**Research recommendations for review questions: For adults with a new episode of less severe depression or more severe depression, what are the relative benefits and harms of psychological, psychosocial, pharmacological and physical interventions alone or in combination?**

### Research question

Is peer support an effective and cost-effective intervention in improving outcomes, including symptoms, personal functioning and quality of life in adults as a stand-alone intervention in people with less severe depression and as an adjunct to other evidence-based interventions in more severe depression?

### Why this is important

Not all people with depression respond well to first-line treatments and for some people the absence of good social support systems may account for the limited response to first-line interventions. A number of models for the provision of peer support have been developed in mental health which aim to provide direct personal support and help with establishing and maintaining supportive social networks, but to date few studies have established and tested peer support models for people with depression.

**Table 103. Research recommendation rationale**

| Research question | Is peer support an effective and cost-effective intervention in improving outcomes, including symptoms, personal functioning and quality of life in adults as a stand-alone intervention in people with less severe depression and as an adjunct to other evidence-based interventions in more severe depression? |
|---|---|
| **Importance to 'patients' or the population** | Depression is a debilitating and highly prevalent condition in adults. Despite significant investment, the most effective and well-established treatments have only modest effects on depressive symptoms, and more effective treatments for acute depression are therefore required. |
| **Relevance to NICE guidance** | Peer support is not currently recommended as there is insufficient evidence for its use. |
| **Relevance to the NHS** | Peer support may be an effective and cost-effective treatment for depression, and its use may therefore lead to reduced costs for treating people with acute depression. |
| **National priorities** | The NHS Five Year Forward plan makes access to effective mental health services a key national priority. |
| **Current evidence base** | There is no available evidence to show the effectiveness of peer support. |
| **Equality** | No equality issues. |
| **Feasibility** | A series of randomised controlled trials would be required to assess the effectiveness of different models of peer support. |
| **Other comments** | None |

**Table 104. Research recommendation modified PICO table**

| Criterion | Explanation |
|---|---|
| **Population** | Adults (18 years or older) with acute episode of depression. |
| **Intervention** | Peer support models, including both individual and group interventions, provided by people who themselves have personal experience of a mental health problem. |

| Criterion | Explanation |
|---|---|
| | Peer support for different severities of depression alone or in combination with evidence-based interventions for the treatment of depression. |
| **Comparator** | Placebo, or other treatments for depression. |
| **Outcomes** | Effectiveness - depressive symptoms, personal functioning, quality of life, any adverse events.<br>Cost-effectiveness. |
| **Study design** | Factorial design (followed by RCTs of revised interventions). |
| **Timeframe** | Follow-up to at least 24 months after completion of the intervention. |
| **Additional information** | Sub-group analysis for older people |

### Research question

What are the mechanisms of action of effective psychological interventions for acute episodes of depression in adults?

### Why this is important

Psychological interventions are complex interventions involving many interacting components and delivery elements. Research is required to identify the mechanisms of action of the effective individual psychological treatments for depression, which would allow for the isolation of the most effective components and the development of more potent, cost-effective and acceptable treatments.

**Table 105. Research recommendation rationale**

| Research question | What are the mechanisms of action of effective psychological interventions for acute episodes of depression in adults? |
|---|---|
| **Importance to 'patients' or the population** | Depression is a debilitating and highly prevalent condition in adults. Despite significant investment, the most effective and well-established treatments have only modest effects on depressive symptoms, and more effective treatments for acute depression are therefore required. |
| **Relevance to NICE guidance** | A wide variety of psychological interventions are recommended for acute episodes of depression, but improved evidence for the effectiveness of specific components could lead to greater clarity in the recommendations. |
| **Relevance to the NHS** | Use of more effective and more cost-effective options may lead to reduced costs for treating people with acute depression. |
| **National priorities** | The NHS Five Year Forward plan makes access to effective mental health services a key national priority. |
| **Current evidence base** | Very little evidence is available which identifies the mechanisms or components of psychological interventions that contribute most to their effectiveness. |
| **Equality** | No equality issues |
| **Feasibility** | This research would require a series of experimental studies to identify potential mechanisms associated with current effective treatments for depression which could then be used to inform the development of new treatments. These novel treatments should then be tested in large scale RCTs against current most effective psychological treatments. This would require an extensive programme of research. |
| **Other comments** | None |

**Table 106. Research recommendation modified PICO table**

| Criterion | Explanation |
|---|---|
| **Population** | Adults (18 years or older) with acute episode of depression. |
| **Intervention** | Psychological interventions analysed in terms of into generic therapeutic components (for example therapeutic relationship, rationale; remoralization), therapy structure (for example session duration, frequency), and specific ingredients. The determination of the active components would depend on testing the presence or absence of individual therapeutic elements. The studies will also need to take into account the impact of any moderators of treatment effect including therapist, patient and environment factors. |
| **Comparator** | Placebo, or other therapeutic components, structures or specific ingredients. |
| **Outcomes** | The research will need to be able to fully characterise the nature and range of depressive symptoms experienced by people and relate these to any proposed underlying neuropsychological mechanisms. |
| **Study design** | Factorial design (followed by RCTs of revised interventions). |
| **Timeframe** | Follow-up to 24 months after intervention. |
| **Additional information** | None |

### Research question

What is the effectiveness and cost-effectiveness of combination treatment with acupuncture and antidepressants in people with more severe depression in the UK?

### Why this is important

There is evidence that combination treatment with acupuncture and antidepressants is effective and cost-effective in more severe depression. However, the evidence for this was based on studies that had been conducted in China, and the committee were aware that Chinese acupuncture may differ from that offered in the the UK. It is therefore important to evaluate the effectiveness of Western-style acupuncture in combination with antidepressants to evaluate if this combination is also effective and cost-effective.

**Table 107. Research recommendation rationale**

| Research question | **What is the effectiveness and cost-effectiveness of combination treatment with acupuncture and antidepressants in people with more severe depression in the UK?** |
|---|---|
| **Importance to 'patients' or the population** | Antidepressants are effective for more severe depression, but people with depression may wish to consider complementary therapies to support improvement in their mood. Acupuncture is not a commissioned service, so only available to people with financial means to pay for them. This may increase health inequalities. |
| **Relevance to NICE guidance** | The existing evidence for the use of acupuncture is based on Chinese acupuncture which may be different from acupuncture delivered in the Western world, so evidence cannot be extrapolated to UK populations. |

| Research question | What is the effectiveness and cost-effectiveness of combination treatment with acupuncture and antidepressants in people with more severe depression in the UK? |
|---|---|
| **Relevance to the NHS** | If effective, acupuncture would need to be commissioned as part of the offer for patients with more severe depression. |
| **National priorities** | Depression is a common condition, impacting on quality of life of people, including work absence.<br>If acupuncture plus antidepressants is shown to be more effective than antidepressants alone, this may reduce incidence of treatment-resistant depression, poorer patient outcomes and referral to specialist care. |
| **Current evidence base** | The evidence-base identified was based on Chinese acupuncture which may be different from acupuncture delivered in the Western world, so evidence cannot be extrapolated to UK populations. |
| **Equality** | Acupuncture is not a commissioned service – so only people with financial means can afford to purchase this intervention. |
| **Feasibility** | It is likely that acupuncture could be a commissioned service within IAPT or social prescribing services. |
| **Other comments** | Acupuncture may be more acceptable than a combination of two antidepressants or other combination of drugs for more severe depression. |

**Table 108. Research recommendation modified PICO table**

| Criterion | Explanation |
|---|---|
| **Population** | Adults (18 years or older) with acute episode of more severe depression. |
| **Intervention** | Western-style acupuncture in combination with antidepressants. |
| **Comparator** | Sham acupuncture + placebo. |
| **Outcomes** | Critical:<br>• Depression symptomatology (PHQ-9)<br>• Remission<br>• Response<br>• Discontinuation due to side effects (for pharmacological trials)<br>• Discontinuation due to any reason (including side effects).<br><br>Important: |

| Criterion | Explanation |
|---|---|
| | • GAD7<br>• Quality of life<br>• Personal, social and occupational functioning. |
| **Study design** | Randomised 3-arm Controlled Trial, plus nested qualitative study to explore acceptability. |
| **Timeframe** | Acupuncture Intervention 6 sessions or 12 sessions (3 arm trial)<br>Follow-up 3, 6 and 12 months, then 24 months after intervention |
| **Additional information** | Nested qualitative study vital to explore acceptability of acupuncture and barriers to implementation in routine care. |

### Research question

What is the incidence and severity of withdrawal symptoms for antidepressant medication?

### Why this is important

The committee found relatively little evidence to provide information for people with depression on the withdrawal symptoms for antidepressant medication and to guide recommendations on the best methods for stopping long-term antidepressant treatment.

**Table 109. Research recommendation rationale**

| Research question | What is the incidence and severity of withdrawal symptoms for antidepressant medication? |
|---|---|
| **Why is this needed** | |
| **Importance to 'patients' or the population** | Antidepressant use is common (more than 10% of adults), and coming off them is difficult for a proportion of people. |
| **Relevance to NICE guidance** | More specific guidance is needed on the likely incidence and severity of withdrawal symptoms and how to minimise them. |
| **Relevance to the NHS** | The NHS spends around £300M per year on antidepressant prescribing, and consultations for prescribing and managing withdrawal are several times more costly than the prescriptions themselves. |
| **National priorities** | All CCGs must, as a minimum, invest in mental health services to meet the Mental Health Investment Standard. |
| **Current evidence base** | A 2018 systematic review suggested that withdrawal symptoms on stopping antidepressants were present in more than half of patients, and severe in around half of those suffering them.<br><br>Davies J, Read J. (2018) A systematic review into the incidence, severity and duration of |

| Research question | What is the incidence and severity of withdrawal symptoms for antidepressant medication? |
|---|---|
| | antidepressant withdrawal effects: Are guidelines evidence-based? (PDF) Addictive Behaviors. 2018 Sep 4. https://doi.org/10.1016/j.addbeh.2018.08.027<br><br>However some of the studies included relied on online retrospective self-reporting of symptoms, which would tend to be biased in the direction of greater problems due to the greater salience of the question to people who did recall withdrawal symptoms.<br><br>A more recent Cochrane review found few studies that examined stopping long-term antidepressants prospectively. A lack of distinction between withdrawal symptoms and relapse in the studies reviewed limited interpretation about the effectiveness and safety of approaches for stopping versus continuing long-term antidepressants.<br><br>Van Leeuwen E, van Driel ML, Horowitz MA, Kendrick T, Donald M, De Sutter AIM, Robertson L, Christiaens T. Approaches for discontinuation versus continuation of long-term antidepressant use for depressive and anxiety disorders in adults. Cochrane Database of Systematic Reviews 2021, Issue 4. Art. No.: CD013495. DOI:10.1002/14651858.CD013495.pub2.<br><br>The review recommended future studies should assess (1) the incidence of withdrawal symptoms in patients tapering antidepressants, (2) identification of risk factors to better predict withdrawal symptoms, and (3) the relative advantages of different dose reduction regimens.<br><br>It has been suggested studies should include tapering SSRI treatment hyperbolically and slowly, in the same way as benzodiazepines are usually withdrawn after a period of prolonged use.<br><br>Horowitz MA, Taylor D. Tapering of SSRI treatment to mitigate withdrawal symptoms. Lancet Psychiatry 2019;6:538-46.<br><br>Ruhe HG, Horikx A, van Avendonk MJP, Woutersen-Koch H. Tapering of SSRI treatment to mitigate withdrawal symptoms. Lancet Psychiatry 2019;6:561-2. |
| **Equality** | NA |
| **Feasibility** | No concerns |
| **Other comments** | NA |

*NA: Not applicable*

**Table 110. Research recommendation modified PICO table**

| Criterion | Explanation |
|---|---|
| **Population** | Adults taking long-term antidepressants for longer than one year for a first episode of depression, or longer than two years for a recurrent episode, who are no longer depressed and wish to come off treatment. |
| **Intervention** | Stopping antidepressants slowly (at a rate set according to patient experience) over several months using hyperbolic tapering. |
| **Comparator** | Stopping antidepressants in uniform steps of a fixed proportion of the starting dose over 1-2 months. |
| **Outcomes** | • Withdrawal symptoms measured using a) the 43-point Discontinuation-Emergent Signs and Symptoms (DESS) checklist, Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WB. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. Biol Psychiatry. 1998 Jul 15;44(2):77-87 and b) self-reporting based on self-definition of withdrawal symptoms.<br>• Successful cessation of antidepressants for two months or more.<br>• Relapse of depression measured using a validated measure of depression symptoms. |
| **Study design** | RCT |
| **Timeframe** | One year |
| **Additional information** | Hyperbolically tapering SSRI treatment is done slowly, in the same way as benzodiazepines are usually withdrawn after a period of prolonged use, taking as long as the patient needs to remain free of major withdrawal symptoms.<br><br>This should be compared with more conventional stepwise reduction, halving the dose and halving it again before stopping altogether.<br><br>Horowitz MA, Taylor D. Tapering of SSRI treatment to mitigate withdrawal symptoms. Lancet Psychiatry 2019;6:538-46.<br><br>Ruhe HG, Horikx A, van Avendonk MJP, Woutersen-Koch H. Tapering of SSRI treatment to mitigate withdrawal symptoms. Lancet Psychiatry 2019;6:561-2. |