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Evidence available for patient-identified priorities in depression research: results of 11 rapid responses

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ABSTRACT

Objectives Patient priority setting projects (PPSPs) can reduce research agenda bias. A key element of PPSPs is a review of available literature to determine if the proposed research priorities have been addressed, identify research gaps, recognise opportunities for knowledge translation (KT) and avoid duplication of research efforts. We conducted rapid responses for 11 patient-identified priorities in depression to provide a map of the existing evidence.

Design Eleven rapid responses.

Data sources Single electronic database (PubMed).

Eligibility criteria Each rapid response had unique eligibility criteria. For study designs, we used a stepwise inclusion process that started with systematic reviews (SRs) if available, then randomised controlled trials and observational studies as necessary.

Results For all but one of the rapid responses we identified existing SRs (median 7 SRs per rapid response, range 0–179). There were questions where extensive evidence exists (ie, hundreds of primary studies), yet uncertainties remain. For example, there is evidence supporting the effectiveness of many non-pharmacological interventions (including psychological interventions and exercise) to reduce depressive symptoms. However, targeted research is needed that addresses comparative effectiveness of promising interventions, specific populations of interest (eg, children, minority groups) and adverse effects.

Conclusions We identified an extensive body of evidence addressing patient priorities in depression and mapped the results and limitations of existing evidence, areas of uncertainty and general directions for future research. This work can serve as a solid foundation to guide future research in depression and KT activities. Integrated knowledge syntheses bring value to the PPSP process; however, the role of knowledge synthesis in PPSPs and methodological approaches are not well defined at present.

Strengths and limitations of this study

- We provide a summary of the existing evidence for 11 patient-identified priority topics in depression research based on rigorous and transparent review methods.
- Our application of rapid review methods is a novel approach to verify uncertainties arising from a patient priority setting project (PPSP).
- This work provides a solid foundation to specify future depression research needs and knowledge translation activities.
- Our lessons learnt from conducting knowledge syntheses for a PPSP will help inform this aspect of the James Lind Alliance methods.
- Further work on whether and how to involve patients in the literature review aspect of a PPSP would be beneficial to ensure their perspectives are integrated throughout the process.

INTRODUCTION

Worldwide, an estimated 300 million people suffer from depression, a mental health disorder that is the primary contributor to global disability.[1] Although more prevalent in older female adults, depression can affect all ages, sexes and ethnicities.[1 2] For the individual, depression negatively affects physical health and well-being, leading to a reduced quality of life while exerting a considerable financial burden on society due to lost productivity, workplace absenteeism and healthcare costs.[2–6]

Historically, the research agenda has not aligned with patient priorities; research agendas are often biased towards commercial interests of funders and personal interests of researchers.[7] For example, registered trials comparing drug efficacies are much more common than those comparing drugs to non-drug therapies (86.3% vs 2.6%), such as antidepressants versus psychotherapy, which may be of more interest to patients.[7] Recently, numerous initiatives have been launched to incorporate the patient voice in health research.[8–10]

Involving patients with lived experience in research priority setting aids in ensuring research agendas reflect the interests of both patients and researchers, increasing the

1. Which treatment therapy or method is more successful for long term remission or recovery?	7. Can diet or exercise affect the development of depression?
2. What are the long term physical implications of pharmacotherapy for treating depression?	8. What are the functional, social, intellectual, physical and psychological problems experienced by children and teens living with an immediate family member who has depression?
3. For various treatment options (e.g. psychotherapy, individual vs. group psychotherapy and psychosocial support), what are the advantages in terms of cost, effectiveness, relapse, prevention and safety?	9. What interventions are effective in preventing and treating workplace depression and reducing stigma associated with depression in the workplace?
4. What are the prevention strategies/tactics for reducing self-harm and suicide in children, youth and adults with depression?	10. Are there structural or functional changes in the brain due to antidepressant therapy during brain development?
5. What changes to the health care system will increase access to psychological services?	11. What is the role of family in the treatment and trajectory of depression?
6. What changes in the health care system will result in shortened wait times for depression services?	

Figure 1 Alberta's top 11 patient-identified depression research priorities.[14]

use and value of subsequent knowledge generation and translation.[7 11 12] With this in mind, the Alberta Strategy for Patient-Oriented Research (SPOR) SUPPORT Unit Patient Engagement Platform, in partnership with the Alberta Health Services Addictions and Mental Health Strategic Clinical Network and the Canadian Depression Research and Intervention Network, undertook the Alberta Depression Priority Setting Project (ADPSP). The aim of the project was to identify Albertans' top research priorities in the area of depression. The ADPSP adapted the James Lind Alliance (JLA) Priority Setting Partnership method to guide the process; detailed methods and results are described elsewhere.[13 14] In summary, the ADPSP undertook five steps: identification of a topic and assembly of participants, gathering of research priorities from a public survey, consolidation of proposed priorities, ranking through a second public survey and a final prioritisation process to produce a list of top 11 priorities in depression research (figure 1).

A key element of any patient priority setting process is a literature review to determine if the proposed research priorities have been previously answered.[15] The Knowledge Translation (KT) Platform of the Alberta SPOR SUPPORT Unit undertook a series of rapid responses to examine the extent and nature of existing evidence relating to the ADPSP's top 11 priorities. The goal was to identify research gaps, recognise opportunities for KT and prevent duplication of research efforts. The purpose of this paper is to detail the available evidence for the patient-identified priorities in depression and to discuss our approach to knowledge synthesis in the context of a patient priority setting project (PPSP).

METHODS

We used rapid review methodology adapted from available guidelines[16] as it is best suited for reviewing a large body of evidence in a short amount of time. As a first step, we worked with the ADPSP colead who was directly involved in the PPSP to identify the PICO components (population, intervention, comparison, outcome) of the priorities and generate researchable questions to guide our syntheses, which is consistent with guidance for conducting PPSPs.[15] We undertook 11 rapid responses of nine priorities suitable for knowledge synthesis. One of the priorities (#3, figure 1) was multifaceted and divided into three subquestions, and two health services questions (#5 and #6, figure 1) were better answered by internal health systems data. Table 1 details each rapid response question, inclusion and exclusion criteria.

Search

Search methods vary for the breadth of available rapid reviews approaches.[17] While the JLA recommends the Cochrane Database of Systematic Reviews and a number of guideline centres, it does not require particular database sources. In consultation with an information specialist, we decided to search PubMed (MEDLINE) as our primary source of evidence as the database indexes reviews (including Cochrane systematic reviews (SRs)), guidelines and trials and provides broad coverage of depression research with over 25 million references to journal articles in life sciences, with a concentration on biomedicine.[18] For each question, we searched PubMed via NCBI Entrez (1946–current) for key concepts (table 1). To moderate the resources required to review a large body of evidence, we determined a priori to filter the available evidence based on hierarchies of evidence and relevance of the study design to the research question. The JLA recommends verifying uncertainties with SRs and adding additional sources with robust methodologies as needed.[15] We started with SRs, then randomised controlled trials (RCTs) and observational (non-randomised) studies. JLA also suggests using up-to-date evidence which has been published in the last 3 years, while the rapid review guidelines we adapted suggest a 5 year date range.[16] We extended it to 10 years to be overly inclusive. Search results were limited to English-language publications from 2007 and were executed for each question between July and October 2017. The search strategies

Table 1 Key questions and inclusion/exclusion criteria

Question	Population	Intervention/Exposure	Comparison	Outcomes	Exclusions
1. Which treatment therapy or method for depression is more successful for long-term remission or recovery?	Participants of any age diagnosed with depression	ADM, psychotherapy alone or in combination	Any other depression treatment	Remission, relapse	Comparisons of individual ADMs or CAMs
2. What are the long-term physical implications of pharmacotherapy for treating depression?	Participants of any age diagnosed with depression	Current or past treatment with any ADM	No ADM treatment or treatment with a different ADM	Long-term (>1 year) physical harms of ADMs	Outcome: Short term harms
3a. For various non-pharmacological treatment options, what are the advantages in terms of cost?	Participants of any age with depression	Psychological treatment (psychotherapy, individual or group therapies, psychosocial support)	Any other psychological treatment	Cost effectiveness of psychological therapies	Comparator: pharmacological treatment, treatment as usual or no treatment.
3b. For various non-pharmacological treatment options, what are the advantages in terms of safety?	Participants of any age with depression	Psychological treatment (psychotherapy, individual or group therapies, psychosocial support)	Any other psychotherapeutic treatment	Safety, adverse events, harms	Comparators of pharmacological treatment, treatment as usual, no treatment or CAMs
3c. For various non-pharmacological treatment options, what are the advantages in terms of effectiveness and relapse prevention?	Participants of any age with depression	Psychological treatment (psychotherapy, individual or group therapies, psychosocial support)	Any other psychological treatment	Progression or severity of depression, relapse	Intervention: depression prevention; Comparator: ADMs, treatment as usual or no treatment
4. What are the prevention strategies/tactics for reducing self-harm and suicide in children, youth and adults with depression?	Participants of any age diagnosed with depression	Suicide or self-harm prevention programmes	None	Suicide attempts and self-harm	Pharmacological interventions
7. Can diet or exercise affect the development of depression?	Participants of any age diagnosed with depression	Intervention related to current or modified dietary intake or exercise	Antidepressant pharmacotherapy or a different dietary or exercise programme	Development, progression and/or severity of depressive symptoms	None
8. What are the functional, social, intellectual, physical and psychological problems experienced by children and teens living with an immediate family member who has depression?	Children and/or adolescent participants 18 years of age or younger living with an immediate family member (parent or sibling living in the same residence) who had been diagnosed with depression	No intervention. Exposure is living with an immediate family member who had been diagnosed with depression	None	Functional, social, intellectual, physical and psychological problems	None

Continued

Table 1 Continued

Question	Population	Intervention/Exposure	Comparison	Outcomes	Exclusions
9. What interventions are effective in preventing and treating workplace depression and reducing stigma associated with depression in the workplace?	Participants of any age with depression	Workplace interventions	None	Change in symptom progression or severity; reduction in stigma	Studies with general outcomes of mental health and psychological well-being that did not specifically report depression outcomes
10. Are there structural or functional changes in brains due to antidepressant therapy during brain development (in children)?	Children and/or adolescent participants 18 years of age or younger diagnosed with depression	Treatment with ADMs	None	Structural or functional development of the brain	None
11. What is the role of the family in the treatment and trajectory of depression?	Participants of any age	Involvement of family members in the patient's management of depression	None	Symptom progression or severity; family's influence on treatment decisions or remission rates	None

ADM, antidepressant medication; CAM, complementary or complementary medicine.

are available in online supplementary appendix 1. Records were managed in EndNote X7 (Clarivate Analytics, Philadelphia, Pennsylvania) and screened in Microsoft Office Excel 2016 (Microsoft, Redmond, Washington, USA).

Study selection

For eight rapid responses, we undertook staged screening by study design (SRs first, then RCTs, then observational studies) dependent on the quantity and level of evidence identified at each stage (figure 2). For three rapid responses, we screened all study designs. Primary screening (title and abstract) followed by secondary full text screening was done by a single reviewer based on a priori eligibility criteria (ie, patient characteristics, intervention/exposure, comparisons and outcome measures) (table 1).

Data extraction and quality assessment

Key study characteristics, general findings and conclusions were extracted by a single reviewer. Included studies were not assessed for quality as the goal was to map all the evidence available rather than answer a specific question based on the best available evidence;[19] however, author-reported study limitations were extracted and included in the summary tables.

Data synthesis

We synthesised the findings narratively and in tabular format and presented conclusions in terms of the quantity and level of the existing evidence and future research needs/priorities.

Patient involvement

Persons with lived experience were members of the ADPSP steering committee and 445 members of the public responded to the ADPSP survey. While the depression research priorities identified by the ADPSP were the foundation of the rapid responses, patients were not involved in the knowledge synthesis process which is consistent with PSP guidance.[15]

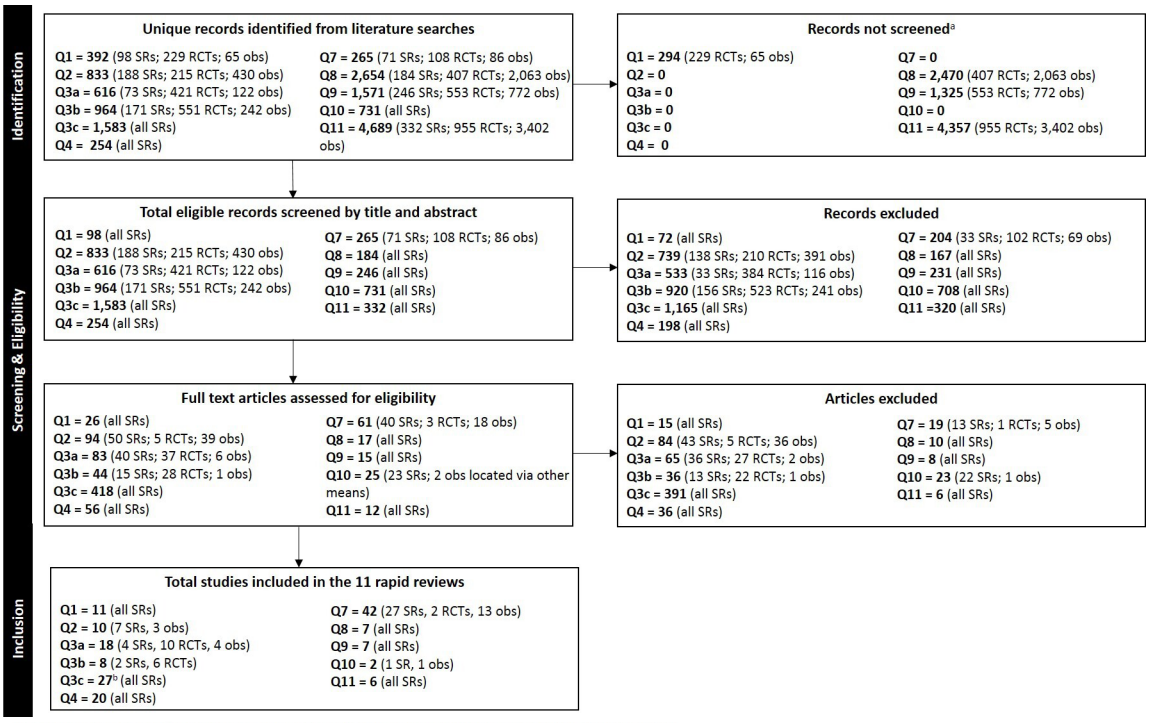
RESULTS

Across the 11 rapid responses, we included 158 studies and identified existing SRs for all but one of the questions (median 7 SRs per rapid response, range 0–179) (figure 2). A narrative summary of the findings of each rapid response is presented below. The conclusions and limitations of the existing evidence and future research needs/priorities are outlined in table 2; details of each included study are available in online supplementary appendix 2.

Q1. Which treatment therapy or method for depression is more successful for long-term remission or recovery?

Remission

The evidence did not support a difference in remission rates among patients treated with antidepressant medication (ADM) compared with cognitive behavioural therapy



Obs: Observational study; **Q:** rapid response question; **RCT:** Randomized controlled trial; **SR:** Systematic review

[a] When extensive data from SRs were identified, we did not screen the RCTs or observational studies identified via the search.

[b] For Q3c, there were 179 SRs containing data relevant to the research question. Of these, the 27 of highest relevance were retained for the review.

Figure 2 Flow diagram of screening decisions. RCTs, randomised controlled trials; SRs, systematic reviews.

(CBT),[20–22] interpersonal psychotherapy,[20 21] psychodynamic therapy[21] or combination therapies (ADM and CBT).[21] One review reported there was insufficient evidence to draw conclusions about ADM effectiveness compared with third-wave CBT.[21] Two reviews found no difference in remission rates between patients with treatment-resistant depression who: were treated with ADM or psychotherapy;[23] switched from ADM to a new ADM or to cognitive therapy (CT)[21] or augmented ADM with a new ADM or with CT.[21] For children and adolescents, there was insufficient evidence to determine the most effective treatment to induce remission.[24]

Relapse prevention

Reduction in relapse risk was found among patients treated with ADM compared with psychotherapy;[25] with psychotherapy (alone or in combination with ADM) after response to ADM;[26] and with augmentation of treatment as usual (with or without ADM) with mindfulness-based cognitive therapy (MBCT).[27] One review found no difference between maintenance ADM and MBCT.[28] For children and adolescents, increased relapse risk was reported among patients treated with ADM alone compared with ADM with CBT.[29]

Q2. What are the long-term physical implications of pharmacotherapy for treating depression?

The observational SR[30–34] findings support a relationship between ADM use and risk of incident fracture that appears to be independent of bone mineral density. Persistence of risk over time is unclear.[30 34] One SR[35] supported an association between ADM use and incident diabetes, and another[36] associated certain ADMs with weight gain, cardiovascular events and fractures. Two cohort studies[37 38] support an association between ADM use and incident cardiovascular risk factors, while one cohort study[39] did not support any association between ADM use and incident hepatocellular carcinoma in adults with hepatitis C.

Q3a. For various non-pharmacological treatment options, what are the advantages in terms of cost?

Considerable heterogeneity in the types of therapies researched precluded meaningful synthesis. The included studies examined 16 different therapies: behavioural activation,[40 41] CBT,[41–54] general counselling,[43] person-centred therapy,[50] problem-solving therapy,[54] psychoanalysis,[45 55] psychoanalytic psychotherapy,[55] psychoeducation,[48 56] CBT-enhanced psychoeducation,[48] psychologist-enhanced psychoeducation,[48] short-term[48 57] and long-term[57] psychodynamic therapy, psychosocial therapy,[45] relaxation therapy,[42] self-management therapy[56] and solution-focused therapy.[48 57] The SRs[42 43 48 51] each included zero to three studies with relevant comparisons that presented economic data.

Across all 18 included studies, there were 22 different cost effectiveness comparisons; two SRs each included three[45] and four[48] relevant comparisons, and only two primary studies investigated the same comparison (telephone vs in-person CBT).[46 47] There were two SRs,[42 51] three RCTs[44 46 47 49 52 53] and three observational studies[44 46 53] that focused specifically on various approaches to the delivery

Table 2 Conclusions, limitations and research needs identified from available evidence for patient-identified priority questions

Question	Number and type of included studies; publication years; total number of studies or participants (median; range)	Conclusions	Limitations	Research Needs
1. Which treatment therapy or method for depression is more successful for long-term remission or recovery?	11 SRs 2007–2016 n=143 studies (2; 1–69 per SR)	Most reviews reported no difference in the risk of remission for patients treated with ADM, psychotherapies or combination therapies. Evidence for the comparative effectiveness of various therapies for preventing relapse is mixed.	Despite the availability of multiple evidence syntheses, many of the review-level comparisons were limited to few RCTs with small sample sizes, often at high risk of bias. Between-study heterogeneity in populations, treatments, length of follow-up and definitions of remission and relapse also hindered the development of strong conclusions.	It appears that there is a need for more robustly conducted, transparently reported trials among children, adolescents and adults comparing various treatments to determine with confidence which therapy is most effective. Subgroup analyses by depression severity and chronicity are needed to inform tailored management strategies.
2. What are the long-term physical implications of pharmacotherapy for treating depression?	6 SRs, 1 review 2010–2015 n=92 studies (14; 12–23 per SR)* 3 Obs 2013–2016 n=6 39 833 participants (109 736; 5145–523 952 per study)	There appears to be extensive evidence from SRs of observational studies supporting a relationship between ADM use and risk of fracture, but a lack of RCTs has limited the ability to infer causality. There appears to be limited evidence from SRs and observational studies for a possible relationship between ADM use and incident diabetes and cardiovascular risk.	Lack of controlling for confounders, heterogeneity in outcome measures, limited number of RCTs (especially those with long-term follow-up).	It remains unclear whether other physical harms of ADMs may exist, as these have not been reported. Randomised trials with long-term follow-up would strengthen the evidence but the feasibility of these is questionable; at a minimum RCTs should include and systematically gather information on adverse effects. For newer ADMs, continued research is needed for evidence related to long-term physical harms.
3a. For various non-pharmacological treatment options, what are the advantages in terms of cost?	4 SRs 2010–2016 n=7 studies (2; 1–3 per SR) 10 RCTs 2007–2017 n=4796 participants (229; 101–2659 per study) 4 Obs 2010–2015 n=40 214 participants (451; 85–39 227 per study)	We identified comparisons of cost effectiveness between a vast array of psychological therapies, though few were supported by more than one study. Comparative cost effectiveness trials are few considering the multitude of available therapies.	Small number of included studies for SRs; methodological limitations (ie, probable confounding, a lack of control groups, high attrition rates and limited generalisability outside of the region in which each therapy was studied).	There is a need for methodologically robust comparative effectiveness trials with cost analyses for the various available therapies (especially those that show promise).

Continued

Table 2 Continued

Question	Number and type of included studies; publication years; total number of studies or participants (median; range)	Conclusions	Limitations	Research Needs
3b. For various non-pharmacological treatment options, what are the advantages in terms of safety?	2 SRs 2013–2015 n=26 studies (13; 1–25 per SR) 6 RCTs 2012–2017 n=2124 participants (327; 34–780 per study)	It appears that most studies comparing psychotherapies for depression do not collect adverse events data. Of those that do, adverse events related to the psychotherapies are infrequently reported. It is possible that data on harms from non-comparative studies exist, but this fell outside the scope of the review.	Neither review identified any studies that reported on adverse events. RCTs were heterogeneous with respect to population and the psychotherapies investigated.	Considering the paucity of data on the comparative harms of psychotherapies for depression, there is a need for more primary research before definitive conclusions about their safety can be drawn. As above. RCTs should regularly include outcomes related to adverse events and employ mechanisms to systematically and rigorously collect these data.
3c. For various non-pharmacological treatment options, what are the advantages in terms of effectiveness and relapse prevention?	27 SRs 2007–2017 n=881 studies (15; 1–198 per SR)	The quantity and breadth of SR evidence indicate a great interest in the comparative effectiveness of various psychological treatments for depression among all age groups. Much of the available evidence suggests no significant difference between the various treatments; when differences were detected, they tended to be minor.	Shortage of head-to-head trials directly comparing various psychotherapies; therefore, in most cases, the quality of the evidence was low or insufficient to draw strong conclusions.	The certainty of the evidence is low or lacking for several therapies. It is unclear where further high quality, adequately powered head-to-head trials would change the conclusions.
4. What are the prevention strategies/tactics for reducing self-harm and suicide in children, youth and adults with depression?	3 Overviews of SRs 2011–2016 n=72 SRs (28; 6–38 per overview) 17 SRs 2009–2017 n=546 studies (19; 1–164 per SR)	Systematic reviews of non-pharmacological strategies for reducing self-harm and suicide exist for all ages, with the majority indicating a potential benefit of psychological interventions on depressive symptoms but limited evidence of benefit for suicidality.	Shortage of studies addressing different age groups and ethnic or racial populations; high heterogeneity with respect to populations and interventions investigated.	The reviews for children and young people provide some conflicting results, suggesting that additional work may be needed to identify the most efficacious strategies. Many studies concluded that additional research is needed to examine multifaceted approaches for older adult populations.

Continued

Table 2 Continued

Question	Number and type of included studies; publication years; total number of studies or participants (median; range)	Conclusions	Limitations	Research Needs
7. Can diet or exercise affect the development of depression?	27 SRs 2009–2017 n=352 studies (14; 3–90 per SR) 2 RCTs 2012, 2015 n=353 participants (177; 80–273 per study) 13 Obs 2009–2016 n=256 930 patients (10 094; 1358–82 643 per study)	There is high-level evidence for the use of exercise as a single or adjunct treatment for depression, with study heterogeneity making it difficult to make firm recommendations for specific populations, amount and type of exercise to produce the greatest patient benefit. A lack of synthesis among dietary studies limit the ability to draw conclusions about diet type or specific diet elements and their role in depression.	High heterogeneity of study quality and types of exercise programme components.	More research on the specific parameters of exercise in each population for effective treatment of depression is needed. While multiple large, observational studies exploring the connection between diet and depression exist, there is a paucity of higher levels of evidence that synthesise the findings. In the existing literature, exercise is approached from the standpoint of treatment for existing depression, and publications examining diet mostly explore its role in development.
8. What are the functional, social, intellectual, physical and psychological problems experienced by children and teens living with an immediate family member who has depression?	7 SRs 2007–2016 n=285 studies (16; 9–193 per SR)	There was limited evidence and discussion of child outcomes as the majority of the reviews focused on treatment options and interventions for the mothers who have depression. This population of children and mothers are often exposed to multiple risk factors such as partner/parental conflict and low socioeconomic status making it difficult to draw any causal associations.	Lack of controlling for confounders.	Studies addressing the impact on children who live with a family member with depression are lacking.
9. What interventions are effective in preventing and treating workplace depression and reducing stigma associated with depression in the workplace?	7 SRs 2009–2016 n=560 studies (17;1–481 per SR)	Workplace interventions appear to have a positive effect on depressive symptoms. There was no single intervention that was identified by the reviews as being the most effective for improving symptoms of depression; however, CBT had the most evidence supporting its effectiveness.	Small number of participants in the studies; inconsistencies in outcome measurements for depression. When absenteeism was used as proxy measure for depression studies had a high risk of bias.	There is evidence supporting a number of effective workplace interventions that would benefit people with depression. Increased awareness and subsequent implementation of these interventions is likely to improve depressive symptoms.

Continued

Table 2 Continued

Question	Number and type of included studies; publication years; total number of studies or participants (median; range)	Conclusions	Limitations	Research Needs
10. Are there structural or functional changes in brains due to antidepressant therapy during brain development (in children)?	1 review 2015 Number of studies not reported 1 Obs 2012 n=15 patients	There is a paucity of human studies addressing the effects of antidepressants on adolescent brain development.	Studies included had a number of confounding factors.	There is a need for primary human research studies in this area before any conclusions can be drawn.
11. What is the role of the family in the treatment and trajectory of depression?	6 SRs 2007–2017 n=95 studies (10; 6–39 per SR)	Involvement of family members in a therapy or psychoeducation intervention with a patient with depression can positively impact the patient's depressive symptoms. The most effective type of intervention has yet to be determined. There were also reported benefits for families, with an improved quality of life for caregivers including a reduction in depressive symptoms.	Small numbers of included studies with significant heterogeneity between studies and varying quality.	It is unclear which types of family intervention have the greatest impact on a patient's depressive symptoms. Research opportunities on the benefits to families should also be considered.

*The non-systematic review did not report the number of studies included.
ADM, antidepressant medication; CBT, cognitive behavioural therapy; Obs, Observational studies; RCT, randomised controlled trial; SR, systematic review.

of CBT. Overall, the RCTs and observational studies were hindered by numerous methodological limitations, and given the disparate nature of the comparisons it is not possible to draw conclusions about the comparative cost effectiveness of various treatment options.

Q3b. For various psychotherapeutic treatment options, what are the advantages in terms of safety?

One SR investigated CBT compared with supportive psychotherapy for adults with depression following traumatic brain injury.[58] Another SR investigated behavioural therapy compared with other psychotherapies for adults with depression.[59] Neither SR identified studies that reported adverse events.

The RCTs were heterogeneous with respect to population and psychotherapies investigated. Populations included adolescent and adult inpatients and outpatients with depression, with and without comorbid conditions. Psychotherapeutic treatments included behavioural activation,[41 60] counselling,[61] various forms of CBT,[41 61–64] psychoanalytical therapy[63] and psychosocial interventions.[63] Two RCTs investigated psychotherapies delivered via different means.[60 64]

One RCT reported no difference in adverse events between a brief psychosocial intervention, CBT and short-term psychoanalytical therapy groups.[63] Another RCT reported adverse events that were possibly or probably related to the psychotherapies.[61] Mild adverse events were reported in the computerised CBT group (n=1) and the face-to-face CBT group (n=2); eight moderate adverse events (eg, increased suicidal thinking) were reported in each group. Serious adverse events (suicide attempts) were reported in the computerised CBT group (n=2) and the face-to-face CBT group (n=1). No other adverse events were reported.

Q3c. For various non-pharmacological treatment options, what are the advantages in terms of effectiveness and relapse prevention?

Included SRs[58 59 65–89] mainly compared psychotherapy or CBT versus other psychotherapies across several populations (eg, children, adolescents, adults, postpartum, older adults). There were also comparisons for varied treatment modalities (eg, online vs face-to-face), formats (eg, individual vs group) and level of therapist training. With some exceptions, the available evidence suggests no significant difference between the treatments under study for post-treatment effectiveness (ie, symptom reduction), remission and continued effectiveness at varying lengths of follow-up (ie, relapse prevention). When differences were noted, the effect estimates were usually small and imprecise.

Despite the large number of SRs, they were limited by a shortage of trials directly comparing various psychotherapies; some therapies were left out entirely. There was less evidence for long-term treatment effects and questions remain about which patients would be best suited to the various treatments.

Q4. What are the prevention strategies/tactics for reducing self-harm and suicide in children, youth and adults with depression?

Children, adolescents and young adults

Eight reviews[90–97] examined interventions grouping children, adolescents and young adults (≤24 years). One SR[96] found that interpersonal psychotherapy reduced depressive symptoms in adolescents, but did not impact suicide. Three reviews[90 91 94] examined school-based interventions for suicide reduction; two overviews[90 91] found some benefit to school-based strategies, while one SR[94] found few studies examining this type of intervention and was unable to draw conclusions. Three SRs[92 93 97] examined psychological interventions. One[92] concluded that psychological strategies hold promise as a suicide prevention strategy in this population; one[93] found minimal support for group-based therapy, while the other[97] argued that group-based therapy might be effective in suicide prevention. One SR[95] examined online and mobile application interventions and could not draw strong conclusions from the single included study.

Adults

Four SRs[98–101] investigated interventions aimed at preventing self-harm and suicide in adults. Two[99 100] found that CBT and dialectical behaviour therapy may be effective at preventing and reducing self-harm in those with previous episodes. One[98] was unable to draw conclusions on the effectiveness of psychotherapy for suicidality, and one[101] found CBT to be an effective treatment for depressive symptoms, but did not have a clear effect on suicidality.

Older adults

Two SRs[102 103] addressed suicidality in older populations (≥60 years). Both found that multifaceted primary care interventions were effective in reducing suicidal behaviour, with one[102] reporting a greater effect in women.

All ages; age not indicated

Six reviews[104–109] targeted multiple age groups or did not specify the age group. One SR[104] found text messaging interventions were effective in patients contemplating suicide. Three SRs[105–107] found psychotherapy-based interventions to be an effective treatment of patients with depression or contemplating suicide, though one[107] noted that the effect did not carry over to adolescents. Two reviews[108 109] concluded that more research is needed on combined therapies to determine the potential synergistic benefits of a multifaceted approach.

Q7. Can diet or exercise affect the development of depression?

Diet

We identified evidence for the role of diet in the treatment or prevention of depression from 2 narrative reviews[110 111] and 13 observational studies.[112–124] One review[110 111] found that the importance of good nutrition for mental health is supported in the literature, especially

for older populations, and the second[110] found that Western diets might be associated with a higher risk of depression. Of the observational studies, two studies[113 116] reported that dietary patterns were not associated with depression risk or development, but one[116] noted that overall caloric intake was inversely related to depression in older people. Three studies[121–123] found that moderate adherence to a certain diet type was associated with lower rates of depression. The remaining studies investigated specific nutrients. Five studies[114 118–120 124] examined fish or the consumption of specific fatty acids. One[120] reported no association between fat intake and depression; another[119] found no relationship between omega-3 polyunsaturated fatty acids (PUFA) and depression, but reported an inverse relationship between α-linoleic acid and depressive symptoms. Two studies[114 118] reported an inverse relationship between depression risk and fish consumption. One study[123] found that higher trans fatty acid consumption was associated with a higher risk of depression, as well as an inverse association between monounsaturated fatty acids, PUFA or olive oil consumption and depression. Of the remaining studies, one[117] found no association between zinc intake and depression risk, one[115] found a moderate positive relationship between dietary fibre intake and depression rates and one[112] reported that higher flavonoid intake may decrease the risk of developing depression.

Exercise and depression

Twenty-five SRs[125–151] provided evidence regarding the role of exercise in the treatment or prevention of depression. Two SRs focusing on adolescents with depression[125 142] found exercise to be effective in reducing depression symptoms. Three SRs found exercise effective for depressive symptoms in elderly patients, with one concluding that exercise had a large antidepressant effect,[149] one finding no difference between exercise and antidepressant drugs[147] and the third finding exercise in conjunction with antidepressants to be effective in elderly patients with treatment resistant depression.[137] Two reviews looked at exercise for depression in special populations, with one finding reduced symptoms in pregnant women,[151] and the other finding the same result in patients with chronic disease.[132] Three reviews found exercise to be effective as an adjunct to other therapy, including pharmacological or psychosocial.[127 138 144] Two reviews[133 136] did not find sufficient evidence to suggest a benefit of exercise. The remaining reviews found exercise a favourable intervention in terms of symptom reduction or relapse prevention, with exercise providing additional benefit over no treatment or demonstrating no difference from pharmacological or psychological treatments.[126 128 130 135 139–141 143 148]

Diet, exercise and depression

Two RCTs[129 150] examined interventions with both dietary and exercise components. The first[129] was a pilot of the later study.[150] While the pilot study found that specific lifestyle recommendations were an effective complement to antidepressant therapy,[129] the larger study did not find the same association.[150]

Q8. What are the functional, social, intellectual, physical and psychological problems experienced by children and teens living with an immediate family member who has depression?

Two SRs[152 153] and a meta-analysis[154] found children had significantly higher IQ scores if their mothers were not diagnosed with postnatal depression. For children with a depressed family member, one SR[153] reported either weak or no evidence for all outcomes while another SR[152] reported that maternal depression was more strongly associated with internalising problems than with negative or positive emotion/behaviour, and with children's general psychopathology than with externalising problems and negative or positive emotion/behaviour.

Four SRs reported on a variety of outcomes. One[155] suggested that chronic maternal depression may play an important role in a child being overweight while another[156] reported that when maternal depression exists, early childhood aggression is more likely to occur. Parental prenatal and postnatal depression was found to be responsible for increasing the mean rate of behavioural and emotional problems[157] and antenatal depression was found to affect children's conduct problems and antisocial behaviours.[158]

Q9. What interventions are effective in preventing and treating workplace depression and reducing stigma associated with depression in the workplace?

Five SRs[159–163] measuring depression directly reported that workplace interventions showed positive effects on depression severity, with one meta-analysis[163] indicating a small effect size. No single intervention was identified as being the most effective for improving symptoms of depression; however, CBT had the most evidence supporting its effectiveness.[159 160]

Workplace absenteeism was used as a proxy depression measure in two reviews.[164 165] One review[164] of workers with major depressive disorder or high levels of depressive symptoms reported that combining a work-directed intervention with a clinical intervention decreased sickness absences. In contrast, an earlier review[165] found insufficient evidence to determine effectiveness of workplace interventions on absenteeism in depressed employees due to high risk of bias and very low quality evidence. We did not find any reviews addressing stigma.

Q10. Are there structural or functional changes in brains due to antidepressant therapy during brain development (in children)?

One narrative review[166] reported that research of the effects of ADM on adolescent brain development was limited to animal models and treatment decisions were often based on adult-specific studies. A prospective cohort study (n=15)[167] supported the use of fluoxetine to achieve normal brain activity in adolescents with depression.

Q11. What is the role of the family in the treatment and trajectory of depression?

Four reviews[76 168–170] addressed populations where the main diagnosis was depression. Three[168–170] of these reviews reported that interventions including one or more family members led to improved depressive symptoms in the patient. The remaining review[76] found that while family therapy appears to be more effective than no treatment, the certainty of its effectiveness is unclear. Two[171 172] additional reviews addressed changes in depressive symptoms through family involvement where depression was an outcome of the primary disease diagnosis. For patients with cancer, couple-based interventions, particularly psychoeducation interventions, led to significant improvements in patients' depression scores,[172] while family-orientated intervention was effective at reducing depression in patients poststroke.[171] Three reviews[168 171 172] also reported the interventions benefited patients' families, with an improved quality of life for caregivers including reduced depressive symptoms.

DISCUSSION

An extensive volume of research relating to depression addresses, either in whole or in part, the 11 research questions that arose from the ADPSP. The extent of available research underscores the importance of this mental health disorder and its far-reaching impact. This mapping of the evidence provides a strong and critical foundation to guide future research and KT opportunities.

Among the patient-identified priorities, there are questions where extensive evidence exists (ie, hundreds of primary studies), yet uncertainties remain. It might be tempting to conclude that 'more research is needed'; however, a close examination of what is known and what remains uncertain is critical to guide implementation of proven strategies and judicious investment in future research efforts. For example, there is evidence supporting the effectiveness of many non-pharmacological interventions (including psychological interventions and exercise) to reduce depressive symptoms. However, targeted research is needed that addresses comparative effectiveness of promising interventions, specific populations of interest (eg, children, minority groups) and adverse effects. Further, attention is needed to ensure appropriate and rigorous methods and explore innovative methodologies (eg, real world evidence, pragmatic trials, big data analytics, network meta-analysis) to make the most efficient use of funds, existing research and available data.

A lack of KT was also recognised in the PPSP process. For some priorities, there is research available to answer patient-identified research priorities, yet they are still being identified as knowledge gaps. For example, cognitive behavioural therapy has evidence supporting its effectiveness in preventing and treating workplace depression. Investment in KT strategies to increase awareness and subsequent implementation of these interventions is critical and should be a priority for funding agencies and other stakeholders.

Strengths

From a service provision standpoint, application of rapid response methods enabled our team to provide the requestor with targeted evidence relating to their priorities. From a methods perspective, our approach allowed for the expedited provision of results within a tight timeframe while using transparent and reproducible methods. Last, the collaboration between our knowledge synthesis team and the PPSP furthers the likelihood that future depression research agendas represent the interests of both researchers and patients.

Challenges

We attempted to categorise the results of each rapid response as to whether further primary research, evidence syntheses or KT was needed based on the JLA definition of a treatment uncertainty. Verification of treatment uncertainties through JLA is based on the reported CI of a recent SR or confirmation that a statistically significant result is also clinically important.[15] The priorities identified by the ADPSP were not all focused on treatment efficacy however, and we were unable to find guidance for other research questions. The complexity of the questions also made it difficult to apply definitions of uncertainty. The identified SRs also had multiple effect estimates within and across different outcomes, comparisons and populations. For example, 25 SRs relating to the exercise component of question seven (diet, exercise and depression development) identified four specific populations (teenagers, older adults, pregnant women, persons with chronic disease) and for question three part a (cost advantages for non-pharmacological treatment options), there were 22 different cost comparisons across 18 studies examining 16 different therapies. In order to answer whether treatment uncertainties exist, the question needed to be very specific with details on population, intervention, comparison and outcome. In addition, many of the questions had multiple components; therefore, at times there was evidence for some but not all components. For question seven, there was high quality evidence supporting exercise for preventing further development of depression symptoms; however, there was very little evidence regarding diet. The extensive volume of evidence also posed challenges. For example, question three, part c (effectiveness of non-pharmacological interventions) identified 179 SRs; given our short timeline, it was necessary to include only the 27 SRs which mostly directly answered the research question. An a priori process for ranking or further categorising large volumes of evidence is recommended.

Lessons learnt

The role of knowledge synthesis in PPSPs is currently not well defined. Detailed guidelines that outline how to balance efficiency and methodological rigour while

determining the existing evidence base for a PPSP are needed. We recommend that knowledge synthesis experts be involved early in the PPSP process. Input into the survey may allow for more details of the populations, interventions, comparisons and outcomes of interest by both the public and the steering committee leading to more specific and answerable research questions. Development of very focused questions will decrease the time needed for literature screening and aid in defining criteria to determine certainty of evidence or KT needs a priori. Focused questions are also more likely to be incorporated into a research agenda, a core PPSP goal.

Limitations

With limited rapid review methods guidance available in 2017, we adapted methods used by the Canadian Agency for Drugs and Technologies in Health (CADTH)[16] and scoping review methodology.[19] While the need for evidence in a short time frame directed our methods, our results should be interpreted in light of some limitations such as searching one database (PubMed), not including grey literature, and using a single experienced screener. According to scoping review methodology,[19] we did not conduct formal quality assessment, rather we reported author-identified limitations of the included studies. Due to the large body of evidence, we filtered the citations using recognised approaches to hierarchies of evidence. We did not involve patients in reframing the questions or in identification and synthesis of relevant literature; this is consistent with existing guidance for PSPs.[15] However, further work on whether and how to involve patients in this aspect of a PSP would be beneficial to ensure their perspectives are integrated throughout the process. Finally, the results of this PPSP may not be generalisable to other jurisdictions. For example, a PPSP was undertaken in the UK in 2014/2015 on the same topic of depression and a comparison with the resulting ten priorities revealed only two similar questions relating to the most successful treatment for depression and the impact on children of having a parent with depression. There were three different questions that addressed similar concepts: access to services, workplace stigma and the role of friends and family.[173]

CONCLUSION

Through 11 rapid responses, we identified an extensive body of evidence addressing patient identified priorities in depression research and identified the strengths and limitations of existing evidence, areas of uncertainty and general directions for future research. This work can serve as a strong foundation to guide future research and KT activities. Integrated knowledge syntheses bring value to the PPSP process and help avoid duplication of research effort. The role of knowledge synthesis in PPSPs is not well defined at present, in particular how to involve patients in this process. Categorising available evidence without focused questions or a priori criteria is challenging and may not support all PPSPs particularly where the scope of priorities is broad.

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