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Identifying and mapping biopsychosocial factors associated with pain in adults with advanced liver disease: protocol for a scoping review

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ABSTRACT

Introduction Pain is highly prevalent in the adult population diagnosed with liver disease. Those progressing to advanced liver disease often experience persistent pain and poor pain relief. There is presently limited guidance for the management of pain and associated symptoms in this population. The current literature lacks attention on how physical, psychological and social domains of liver disease modulate the pain experience. In this paper, we outline our scoping review protocol to systematically review the literature from academic bibliographic databases and grey sources to identify and map the biopsychosocial factors associated with pain in adults with advanced liver disease.

Methods and analysis Arksey and O'Malley's methodology, and Tricco *et al*'s Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews, will guide the process for this scoping review. The literature search will include electronic and hand-searching methods using scholarly and grey sources. Scholarly databases include Medline, Embase, Allied and Complementary Medicine and Cumulative Index to Nursing and Allied Health Literature. Grey databases will focus on research studies not captured in the scholarly databases including those by government agencies and professional organisations. Two members of the research team will independently screen the resulting publications following specific inclusion and exclusion criteria. Quality appraisal of the included research studies will employ the use of the Mixed Methods Appraisal Tool version 2018. Data collection and extraction of study characteristics will use a data extraction tool developed iteratively by the research team. Analysis of the factors associated with pain outcomes will be mapped and described according to the domains of the biopsychosocial model of pain.

Ethics and dissemination The scoping review involves analysis of the published literature on pain and advanced liver disease and does not require ethics approval. The results will be shared with expert stakeholders to help establish clinical significance. We will disseminate the findings through publication in a scholarly journal: local, provincial, national and international scientific and professional conferences.

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Strengths and limitations of this study

- A rigorous and detailed search strategy that includes four academic electronic database sources and sources of grey literature.
- This scoping review protocol proposes a systematic method for collating, summarising and reporting results according to the biopsychosocial framework.
- The proposed stakeholder consultation can enhance the relevance and contextualise the findings of the final scoping review.
- This protocol will only include research studies whose participants are adults and literature published in English.
- The findings from this review will inform the basis for future pain research in patients with advanced liver disease.

BACKGROUND

Liver disease is a significant public health problem in Canada and internationally. Global prevalence estimates suggest that 25% of the general population have some form of liver disease.[1 2] As many as two million deaths yearly are attributed to liver disease worldwide and half of those are due to complications of cirrhosis.[3 4] While there are limited data specifying the prevalence of liver disease in Canada, the Canadian Liver Foundation[5] reports that approximately 3 000 000 people are living with liver disease. Between 2012 and 2016, Canadian liver-related deaths grew by 18%, thereby representing a growing burden of disease.[6]

Liver disease comprises many conditions including alcohol-associated, non-alcoholic (fatty liver disease and steatohepatitis), viral hepatitis, drug-induced, cholangitis, genetic and other forms (eg, Wilson's disease).[2 3] These conditions can lead to debilitating disease symptoms and complications requiring intensive clinical management[4 7] For the purposes

of this scoping review, the term *advanced liver disease* will be used to include adult patients with chronic liver disease leading to cirrhosis having decompensated liver failure (ie, end-stage liver disease) that excludes asymptomatic chronic hepatitis and asymptomatic chronic liver disease.[7 8] Decompensated cirrhosis is a term referring to physiologically visible symptoms (eg, ascites) and clinically relevant complications (eg, hepatic encephalopathy)[7 8] requiring inpatient and outpatient management.[9–11]

Patients with advanced liver disease are known to have high healthcare utilisation and costs because of a significant symptom burden and progressive disease trajectory.[12] Up to 79% of patients report pain, which is an independent predictor of clinic visits, phone calls and hospitalisation in outpatients.[13] Many patients with advanced liver disease will experience pain exacerbation towards the end of life. However, patients report their pain is not well relieved.[14] These data underscore the importance of optimising pain management as a means of increasing health-related quality of life and decreasing healthcare utilisation costs among these patients.

Patients with advanced liver disease report a wide array of pain problems including visceral, somatic and psychological sources.[15–17] Visceral pain may arise from inflammation of the liver capsule contributing to regional or referred pain. Lang *et al*[9] differentiate somatic pain into joint, muscle, skin and generalised body pain. Decompensated cirrhosis represents the irreversible late stage of chronic progressive liver disease; it is characterised by ascites, muscle cramps, back pain, pruritus and headaches.[9–11] Advanced liver disease is also accompanied by important psychological symptoms that are known to amplify the experience of pain. Reported psychological symptoms include anxiety, irritability, depression, delirium and fatigue.[9 16 18] Unmediated psychological distress is a predictor of poor coping, quality of life and disability in people with pain.[19] Poorly managed pain symptoms may also pose negative consequences for the patient's social and familial support network. Chronic pain can lead to low levels of physical functioning, thereby promoting a sedentary lifestyle and social isolation.[20] Physical disability and social dependency produced by chronic pain may require family members to undertake increasing caregiver responsibilities. Lack of effective pain treatments may contribute to caregiver strain and impair patient–family relations.[20]

One of the reasons patients with advanced liver disease may experience poor pain control is due to a narrow conceptualisation of pain as a biological, that is, physical phenomenon. The biopsychosocial framework is a conceptual model which proposes that psychological and social factors must be evaluated, along with the biological factors, in the management of pain.[21] According to this perspective, treatment focused on the pathology initiating pain, as well as on providing the patient with techniques to gain a sense of control over psychological and social effects of pain, provide optimal outcomes. This may be a particularly important framework for patients with advanced liver disease who may not tolerate biologically targeted therapies due to concerns about altered medication pharmacokinetics that can precipitate hepatic encephalopathy (eg, opioids, benzodiazepines, acetaminophen) and renal injury (eg, non-steroidal anti-inflammatory agents).[22] Scant emphasis has been given to advanced liver disease pain management approaches based on the biopsychosocial model which are demonstrated to be both clinically effective and cost effective in other populations with serious pain.[23]

The goal of this scoping review is to identify and map biopsychosocial factors associated with pain to clarify established areas of research activity in addition to areas of research where there is little activity. To our knowledge, a review comprising a biopsychosocial lens has not been previously applied to pain research in advanced liver disease.

METHODS

We aim to provide a comprehensive overview of this field and systematically map key concepts, main sources and types of evidence, and research gaps in the literature. We consider a scoping review to be the most suitable approach to identify the range of evidence available in this broad topic area. The development of this scoping review protocol is grounded in Arksey and O'Malley's[24] seminal work with advancements by both Levac *et al*[25] and Colquhoun *et al*.[26] Tricco *et al*'s[27] Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) informs our plan for data charting, critical appraisal of individual sources of evidence and reporting of results.

Stage 1: identifying the research question

We aim to answer the following questions for patients with advanced liver disease:

1. What is the prevalence and classification of pain (eg, acute, chronic, visceral, somatic, neuropathic)?
2. What are the common characteristics of pain (eg, intensity, quality, location, associated features)?
3. What physical, psychological, and social factors are associated with pain?
4. How do recommended pain assessment and management strategies map onto the biopsychosocial conceptual framework?
5. What gaps exist in the literature to aid the planning of future pain research?
6. What is the quality of the evidence from the included studies in this scoping review?

Stage 2: identifying relevant studies

Eligibility criteria

We will use the Population, Concepts, and Context (PCC) domains as the eligibility criteria. PCC is used to foster broad exploration of a clinical problem for guiding a systematic literature search.[28] We will include all primary research study designs. Quantitative (eg, randomised

Table 1 Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	► Adults≥18 years of age. ► Primary diagnosis of advanced liver disease, advanced chronic liver disease, liver failure, end-stage liver disease, decompensated liver disease or decompensated cirrhosis. ► Presence of physical (eg, joint pain, muscle cramps, skin discomfort, generalised body pain, ascites, back pain, pruritus and headache) or psychological (eg, anxiety, irritability, depression, fatigue, mental health disorders, substance use disorders and emotional distress) or social (eg, activity interference) symptoms associated with pain.	► Patients<17 years of age. ► No identified diagnosis related to liver disease. ► Hepatocellular carcinoma, cancer metastases, compensated cirrhosis and liver transplant recipients. ► Absence of physical or psychological symptoms associated with pain.
Concept	► Prevalence of pain. ► Classification of pain. ► Pain characteristics. ► Pain assessment. ► Pain management. ► Observed or self-reported physical, psychological or social determinants of pain. ► Report that relates to the assessment or management of pain.	► No discussion on either prevalence of pain, classification of pain, pain characteristics, pain assessment, observed or self-reported physical, psychological or social determinants of pain. ► Lack of pain assessment and management discussion.
Context	► Research studies dated 1 January 1990 to May 2019. ► Research studies from any geographical location, healthcare setting and sociocultural influence. ► Research studies that are available in English. ► Research studies that are available in full text.	► Research studies dated 31 December 1989 and older. ► Non-English research studies. ► Research studies that are not available in full text.
Study design	► Primary source research studies involving human participants. ► Quantitative studies (eg, randomised controlled trials, before and after studies, cohort and case studies). ► Qualitative studies (eg, ethnography, phenomenological, grounded theory and descriptive studies). ► Mixed-method studies (eg, sequential, convergent designs).	► Non-primary source research studies that provide summaries and do not introduce any new knowledge (eg, literature reviews, topical reviews, commentaries, opinion papers). ► Research studies not involving humans (eg, animal, cellular). ► Presentation abstracts (eg, oral, poster, conference).

controlled trials, before and after studies, cohort and case studies), qualitative (eg, ethnography, phenomenological, grounded theory and descriptive studies) and mixed-method studies exploring biopsychosocial factors impacting pain outcomes in patients with liver disease. Literature reviews, conference abstracts, protocols and commentary documents will not be included since they do not directly respond to the protocol objectives. The search will be limited to studies published between 1990 to May 2019 to allow for a comprehensive inclusion of studies of over 25 years. Non-English language studies will be excluded. To address the PCC, the eligibility criteria will be specific (see table 1).

Information sources

To identify potentially relevant documents, the sources of information will include scholarly and grey literature. Scholarly literature are documents that are research focused and published in peer-reviewed journals. The search for literature will include Medline, Embase, Allied and Complementary Medicine (AMED), and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases. Grey literature are forms of evidence that are published outside of the traditional academic avenues.[29] We will use the Canadian Agency for Drugs and Technologies in Health's[29] guide to systematically search for materials outside of the scholarly databases and will target government agencies and professional organisations. Government agencies will be limited to Canadian agencies for contextual relevance including Canadian Institute of Health Information, Health Canada, Statistics Canada and Canada's Provincial/Territorial Ministries of Health (eg, British Columbia, Ontario, Northwest Territories). Professional organisations will include the Canadian Liver Foundation, American Association for the Study of Liver Diseases, International Association for the Study of Pain and World Health Organization.

Table 2 Sample Medline search strategy

#	Searches
1	pain.tw,kf.
2	((abdominal or acute or arthralgi* or joint or back or muscle or musculoskeletal or general* body or chronic or flank or headache or nociceptive or intractable or postoperative or procedural or referred or persistent or constant or consistent or visceral or somatic or psychosomatic or regional) adj1 pain).tw,kf.
3	(anxiety or irritability or irritable or depression or depressed or fatigue or tired or tiredness or anger).tw,kf.
4	(ascites or cramp*).tw,kf.
5	((hepatic or liver) adj1 encephalopathy).tw,kf.
6	(quality of life or symptom).tw,kf.
7	or/1–6 [Concept 1=Pain]
8	end stage liver disease.tw,kf.
9	(diseas* adj1 liver).tw,kf.
10	((liver or hepatic) adj1 failure*).tw,kf.
11	(dysfunction* adj1 liver).tw,kf.
12	cirrhos*.tw,kf.
13	((decompensate* or liver or hepatic) adj1 cirrhos*).tw,kf.
14	((liver or hepatic or failure*) adj1 decompensate*).tw,kf.
15	(fibros* adj1 liver).tw,kf.
16	or/8–15 [Concept 2=Liver Disease]
17	((management* or intervention*) adj1 pain).tw,kf.
18	((non-pharmacological or nonpharmacological) adj2 pain).tw,kf.
19	(transcutaneous electrical nerve stimulation or tens or acupuncture or electroacupuncture or acupressure or warming or heat).tw,kf.
20	(pharmacolog* adj2 pain).tw,kf.
21	(acetaminophen or nsaid* or nonsteroidal anti-inflammatory drug* or nonsteroidal antiinflammatory drug* or antidepressant* or anticonvulsant* or anesthetic* or anaesthetic* or opioid* or snri or serotonin-norepinephrine reuptake inhibitor* or serotonin norepinephrine reuptake inhibitor* or tramadol or hydrocodone or oxycodone or morphine or hydromorphone or oxycodone or morphine or hydrocodone or methadone or codeine or fentanyl or meperidine or marijuana or analgesic*).tw,kf.
22	paracentesis.tw,kf.
23	((measurement* or scale* or assessment* or questionnaire* or test* or analog or visual or visual analog*) adj1 pain).tw,kf.
24	(health related quality of life or hrqol or quality of life or qol).tw,kf.
25	or/17–24 [Concept 3=Pain Management]

Search strategy

The search strategy for this scoping protocol was developed in collaboration with a health sciences librarian (see table 2). The search strategy for scholarly and grey literature will focus on the concepts of pain (physical, psychological and social factors) and advanced liver disease (this includes all diagnoses such as advanced chronic liver disease, liver failure, end-stage liver disease, decompensated liver disease and decompensated cirrhosis.). The process for searching the scholarly electronic databases of Embase, AMED, and CINAHL will use translation from the Medline search strategy as the basis for concepts. The translation of keywords and medical subject headings terms may vary among the databases. A similar process will be followed for the grey literature.

Stage 3: study selection

Selection of the sources of evidences will involve two independent reviewers using inclusion and exclusion criteria (see table 1). First, the reviewers (first and second author) will screen the title and abstract of the literature using EndNote X9 software as well as an online citation management programme (Covidence) for relevance. The strategy reported by Bramer *et al*[30] for deduplicating will be applied. Second, both reviewers will independently perform a full-text review of the included literature in more depth. Conflicts regarding inclusion will involve discussions between the two independent reviewers, and if needed, a third reviewer (sixth author) who will facilitate the discussion towards inter-rater agreement.

Box 1 Data charting tool

- Study design
  - Type of study (qualitative, quantitative or mixed design)
  - Focus of the study (research questions and objectives)
  - Participant criteria (characteristics (in-terms of age, sex, diagnosis), inclusion and exclusion criteria)
  - Study setting (country, institutional or non-institutional setting, single or multisite)
- Data collection
  - Participant recruitment
  - Methods for collecting information
- Data analysis
  - Methods for analysing the data
  - Procedural information for data analysis
  - Theory or framework of the research study
- Results/outcome
  - Participant characteristics (age, diagnosis, gender)
  - Pain typology (eg, classification, prevalence, characteristic)
  - Biopsychosocial factors of pain (eg, physical, psychological, sociocultural)
  - Pain assessment and management (eg, physical, psychological, sociocultural)

Stage 4: charting the data

The research team will develop a standardised data charting tool informed by the PRISMA-ScR checklist to extract biographical information and study characteristics from full-text articles.[27] The first and second authors will independently extract data from the included studies. The charting process will employ the standardised data charting tool to capture key concepts and detailed information from the full-text articles. Data to be extracted are listed in box 1.

To foster reliability during data extraction, the two independent reviewers will pilot test the data charting tool with 30% of various study types. The data charting tool will undergo calibration with the research team following pilot testing for any relevant changes needed.[27] Considering that a scoping review is an iterative process, the data charting process tool may be altered to accommodate unexpected findings. Extracted data from the research studies will be merged into a single electronic Excel summary document.

Quality assessment

We aim to appraise the quality of included studies using the Mixed Methods Appraisal Tool (MMAT) version 2018. This tool allows the research team to appraise the methodological quality of each study including the research questions, study design, information source and interpretation of the findings.[31] The strength of MMAT is its ability to assess quantitative, qualitative and mixed-method empirical evidence simultaneously without having to rely on different tools.[30] While the MMAT will not be used to exclude studies, it will be used to explore the quality of the evidence.

Data availability

All data relevant to the study are included in the article or uploaded as supplementary information.

Stage 5: collating, summarising and reporting of results

Turk and Gatchel's[21] biopsychosocial conceptual framework will guide the collating and analysis of the information from the scoping review. The prevalence of pain will be reported as a descriptive statistic. The classification of pain will be identified descriptively as acute and/or chronic; visceral and/or somatic; neuropathic and/or some other classification. The pain characteristics will be listed according to identified source of the pain (if known), intensity, duration, quality description, location and any associated features (eg, interference with activities of daily living). Determinants of pain will be categorised into the physical, psychological and sociocultural domains. Similarly, pain assessment and management will be categorised into physical, psychological and sociocultural domains.

The final scoping review will follow PRISMA-ScR guidance which outlines a stepwise framework for a comprehensive, transparent and systematic reporting of the scoping review findings.[27] A summary of key concepts will use numerical and descriptive statistics to outline the number of articles found, screened and included in the scoping review using the PRISMA flow chart.[27] A detailed narrative summary of key information from the included studies will be presented in a table format based on the data charting form. These findings will be supported by a narrative description outlining the key concepts of pain classification, determinants of pain and related pain assessments and management. The biopsychosocial conceptual framework will facilitate the mapping of the key concepts. The review will discuss the findings within the context of the included literature.

Step 6: consultation with stakeholders and knowledge translation

This review will include consultation with interprofessional clinicians involved in the direct care of patients with advanced liver disease. Consultation provides an opportunity to contextualise the findings from this scoping review where the interprofessional clinicians can provide content expertise and meaningful perspectives.[25] The authors will involve members of a regional liver network of interprofessional clinicians in Ontario, Canada, to discuss the relevance of the scoping review results. We will disseminate the findings through publication in a scholarly journal; local, provincial, national and international scientific and professional conferences. The findings from this review will inform the basis for future pain research and the advancement of pain assessment and management for patients with advanced liver disease.

Patient and public involvement

The development of this scoping review protocol did not involve patients or the public. However, the findings

will be shared with stakeholders (ie, clinicians, patient representatives) for significance, feedback and contextual relevance. If patients, patient advocates, researchers and clinicians agree to be involved in the consultation stage, then the details of this will be reported in the final scoping review.

DISCUSSION

The aim of this scoping review is to identify and map biopsychosocial factors associated with pain in adults with advanced liver disease. The biopsychosocial model views pain as the result of the dynamic interaction among physical, psychological and social factors. Pain is a frequent reason for patients with liver disease to seek medical assistance and the provision of pain relief is a central task of healthcare providers. However, pain is a common, undertreated symptom in patients with advanced liver disease and is associated with increased healthcare utilisation. The nature of advanced liver disease limits the use of biologically targeted pain treatments, especially opioids, due to impaired liver metabolism and the risk of adverse drug reactions.[22] Poor pain management in patients with advanced liver disease demonstrates the need to explore potentially modifiable determinants of but not limited to the physical domain. Psychological, and social factors comprise important additional targets for investigation and knowledge development in our review.

Rigorous and novel methodology distinguishes our approach from the prior reviews of pain in the liver disease population.[15 32] Our search strategy involving multiple scholarly databases and the grey literature will provide a more comprehensive understanding of completed research. Turk and Gatchel's[21] theoretical framework will offer a unique perspective into the organisation, classification and conceptualisation of pain. Moreover, by mapping pain assessment and treatment recommendations to the biopsychosocial model, this scoping review will identify new opportunities to align pain appraisal and management strategies with scientific recommendations. The timing of our review is important as the global burden of advanced liver disease is expected to rise; therefore, the problem of pain will increase in proportion. Our approach will broaden views to the identifiable factors associated with pain in patients with advanced liver disease and encourage clinicians and researchers to develop and implement multidimensional assessment and management strategies needed for effective pain relief in this growing population.

In summary, this scoping review will identify and map biopsychosocial factors associated with pain in advanced liver disease to clarify established areas of research activity in addition to areas of research where there is little activity. Our scoping review protocol builds on prior research through a unique, comprehensive and theoretically informed design with key deliverables necessary to guide innovative patient-oriented pain practice and research investment.[32] Our review will be of value to the interprofessional clinical community working with patients with advanced liver disease, funders of liver research, as well as the larger pain community given our rigorous application of a multidimensional pain model.

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Contributors All authors have made substantive intellectual contributions to the development of this protocol. FG and CD conceptualised the review approach and provided general guidance to the research team. FG, CD, MP, DW and EL were involved in developing the review questions and the review design. FG and LI initially developed the data extraction framework which was then further developed by input from team members. FG and CD initiated the first draft of the manuscript which was then followed with substantial input from all of the authors. All authors approved the final version of the manuscript.

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REFERENCES

1 Estes C, Anstee QM, Arias-Loste MT, *et al*. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. *J Hepatol* 2018;69:896–904.
2 Younossi ZM, Koenig AB, Abdelatif D, *et al*. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016;64:73–84.
3 Mokdad AA, Lopez AD, Shahraz S, *et al*. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. *BMC Med* 2014;12:145.
4 Asrani SK, Devarbhavi H, Eaton J, *et al*. Burden of liver diseases in the world. *J Hepatol* 2019;70:151–71.
5 Canadian Liver Foundation. Liver disease in Canada a crisis in the making: an assessment of liver disease in Canada based on available data, 2013. Available: https://www.liver.ca/wp-content/uploads/2017/09/CLF_LiverDiseaseInCanada_Synopsis_E.pdf [Accessed 9 Jul 2019].
6 Statistics Canada. Leading causes of death, total population, by age group (table: 13-10-0394-01). Available: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310039401 [Accessed 24 Apr 2019].
7 Mauss S, Berg T, Rockstroh J, *et al*. *Hepatology: a clinical textbook*. 9th edn, 2018. https://www.hepatologytextbook.com/
8 American Liver Foundation. The progression of liver disease, 2017. Available: https://liverfoundation.org/for-patients/about-the-liver/the-progression-of-liver-disease/#1503432933768-040e8645-d918 [Accessed 9 Jul 2019].

9 Lang CA, Conrad S, Garrett L, *et al*. Symptom prevalence and clustering of symptoms in people living with chronic hepatitis C infection. *J Pain Symptom Manage* 2006;31:335–44.
10 Goldberg E, Chopra S. Cirrhosis in adults: overview of complications, general management, and prognosis. Uptodate, 2018. Available: https://www.uptodate.com/contents/cirrhosis-in-adults-overview-of-complications-general-management-and-prognosis [Accessed Jan 2019].
11 Hamilton JP, Goldberg E, Chopra S. Management of pain in patients with advance chronic liver disease or cirrhosis. Uptodate, 2019. Available: https://www.uptodate.com/contents/management-of-pain-in-patients-with-advanced-chronic-liver-disease-or-cirrhosis?topicRef=86296&source=see_link [Accessed Jan 2019].
12 Kelly EM, James PD, Murthy S, *et al*. Health care utilization and costs for patients with end-stage liver disease are significantly higher at the end of life compared to those of other decedents. *Clin Gastroenterol Hepatol* 2019;17:2339–46.
13 Rogal SS, Winger D, Bielefeldt K, *et al*. Healthcare utilization in chronic liver disease: the importance of pain and prescription opioid use. *Liver Int* 2013;33:1497–503.
14 Madan A, Barth KS, Balliet WE, *et al*. Chronic pain among liver transplant candidates. *Prog Transplant* 2012;22:379–84.
15 Peng J-K, Hepgul N, Higginson IJ, *et al*. Symptom prevalence and quality of life of patients with end-stage liver disease: a systematic review and meta-analysis. *Palliat Med* 2019;33:24–36.
16 Potosek J, Curry M, Buss M, *et al*. Integration of palliative care in end-stage liver disease and liver transplantation. *J Palliat Med* 2014;17:1271–7.
17 Rogal SS, Winger D, Bielefeldt K, *et al*. Pain and opioid use in chronic liver disease. *Dig Dis Sci* 2013;58:2976–85.
18 Coggins CC, Curtiss CP. Assessment and management of delirium: a focus on hepatic encephalopathy. *Palliat Support Care* 2013;11:341–52.
19 Dwight MM, Kowdley KV, Russo JE, *et al*. Depression, fatigue, and functional disability in patients with chronic hepatitis C. *J Psychosom Res* 2000;49:311–7.
20 Dueñas M, Ojeda B, Salazar A, *et al*. A review of chronic pain impact on patients, their social environment and the health care system. *J Pain Res* 2016;9:457–67.
21 Turk DC, Gatchel RJ. *Psychological approaches to pain management: a practitioner's handbooks*. 2nd edn. New York: The Guildford Press, 2002.
22 Walling AM, Wenger N. Palliative care: end-stage liver disease. Uptodate. Available: https://www.uptodate.com/contents/palliative-care-end-stage-liver-disease [Accessed Jul 2019].
23 Gatchel RJ, McGeary DD, McGeary CA, *et al*. Interdisciplinary chronic pain management: past, present, and future. *Am Psychol* 2014;69:119–30.
24 Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Methodol* 2005;8:19–32.
25 Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. *Implement Sci* 2010;5:1–9.
26 Colquhoun HL, Levac D, O'Brien KK, *et al*. Scoping reviews: time for clarity in definition, methods, and reporting. *J Clin Epidemiol* 2014;67:1291–4.
27 Tricco AC, Lillie E, Zarin W, *et al*. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med* 2018;169:467–73.
28 Joanna Briggs Institute. The Joanna Briggs Institute Reviewer's manual 2015: methodology for JBI scoping reviews.. Available: http://joannabriggs.org/assets/docs/sumari/Reviewers-Manual_Methodology-for-JBI-Scoping-Reviews_2015_v2.pdf [Accessed Feb 2019].
29 Canadian Agency for Drugs and Technologies in Health. Grey matters: a practical tool for searching health-related grey literature. Available: https://www.cadth.ca/resources/finding-evidence/grey-matters [Accessed Jan 2019].
30 Bramer WM, Giustini D, de Jonge GB, *et al*. De-duplication of database search results for systematic reviews in endnote. *J Med Libr Assoc* 2016;104:240–3.
31 Hong QN, Pluye P. Mixed methods appraisal tool (MMAT) version 2018 user guide. Registration of Copyright (#1148552), Canadian Intellectual Property Office, Industry Canada. Available: http://mixedmethodsappraisaltoolpublic.pbworks.com/w/file/fetch /127916259/MMAT_2018_criteria-manual_2018-08-01_ENG.pdf [Accessed Mar 2019].
32 Klinge M, Coppler T, Liebschutz JM, *et al*. The assessment and management of pain in cirrhosis. *Curr Hepatol Rep* 2018;17:42–51.