Complementary and alternative therapy (CAM) in haemophilia pain management: a review of published literature

Angela Lambing, Michelle Witkop, Thomas J. Humphries

Pain continues to be a significant issue for people with haemophilia (PWH), whether it is acute pain from a joint bleed, a needle stick when receiving clotting factor treatment, or chronic pain from chronic synovitis and arthritic changes. In the US, there has been controversy and uncertainty regarding the use of oral medications and opioids for the management of chronic pain, including haemophilia pain. Both PWH and their clinicians have started to explore nonpharmacologic options for managing pain, with many PWH trying to limit their use of oral pain medication and using alternative methods. There is little research around the use of complementary and alternative medicine (CAM) for pain management in the haemophilia community. This paper aims to provide a comprehensive literature review of current English language research on the use of therapies that fall into four distinctive domains of CAM in PWH. English language articles were obtained via searches in Medline, Embase and CINAHL using the target search words “haemophilia” or “bleeding disorders” in combination with other search terms relating to CAM. All references were considered regardless of year. Twenty-three CAM articles that included PWH or other bleeding disorders were identified; ten were evidence based while the remainder provided case reports and descriptions of CAM use in PWH. This indicates that there is limited current research in the area of CAM use for pain management in PWH. Evidence of the benefit of CAM is seen in studies of its use to treat pain in other conditions and health-related circumstances. Additional evidenced-based CAM research is needed so that alternative pain management therapies can be utilised in a safe and beneficial manner in PWH.

Keywords: Acute pain, bleeding disorders, chronic pain, complementary alternative medicine (CAM), haemophilia, nonpharmacological
Whether from an acute joint bleed or chronic haemarthritic damage from repeated joint bleeding over time, pain is a known complication of haemophilia. The incidence of persistent pain in the haemophilia population ranges from 15% to 73% [1-4], with an average self-reported pain level of between 4 and 6 on a 10-point pain scale [4]. Timmer et al. reported that symptoms of acute haemarthrosis and haemophilic arthropathy were similar, including pain, swelling, fixed flexed position, reduced range of motion, stiffness and warmth [5]. This suggests that people with haemophilia (PWH) have difficulty in determining the difference between pain experiences – a finding initially reported by a national study of pain among PWH in the United States [4], and further validated in young adults by the IMPACT Quality of Life (QoL) study [6]. Further evaluation of the IMPACT QoL data in PWH aged 13–25 years identified the average reported age of pain management initiation was 11.5 years, despite this being a patient population who have benefited from lifelong prophylaxis. Additionally, a discrepancy between the patients’ self-reported pain level compared to their caregivers’ and providers’ perception of their pain was documented.

Both pharmacologic and nonpharmacologic strategies have a role in the management of acute and chronic pain [7], and PWH are becoming more interested in nonpharmacologic pain management, including complementary and alternative therapy (CAM) options. The use of CAM has been documented in the literature, where 38% of adults and 12% of children with non-cancer chronic pain in the United States sought alternative strategies to manage pain effectively [8]. Many people reportedly seek CAM as they feel that medical treatments do not always help, they wish to avoid potential side-effects of pain medication, or they seek to manage their pain in a more holistic manner [9].

Jadhav et al. identified 42.3% of PWH using CAM in a registry of 160 persons with a bleeding disorder, who cited the main reasons for its usage as to reduce bleed frequency, manage pain and control bleeding episodes [10]. It has also been reported that patients who experience pain now seek a more comprehensive approach to pain management, as they feel it is patient-centred and promotes self-management of their condition as well as treatment [11].

Various reference guides for practitioners on pain management in PWH are available through national and international organisations such as the United States National Hemophilia Foundation (NHF) [12], the Canadian Hemophilia Society [13] and the World Federation of Hemophilia [14], and through comprehensive articles [15,16]. However, few in-depth reviews of CAM pain options specific to PWH within a randomised study design are available.

This paper aims to provide a comprehensive literature review of current English language research on the use of CAM in PWH, taking into account its four distinct domains.

**DEFINING CAM**

CAM is a group of diverse medical and healthcare systems, practices and products that are not presently considered to be part of conventional medicine [17]. The United States’ National Center for Complementary and Integrative Health (NCCIH) defines complementary medicine as a non-mainstream practice used together with conventional medicine, and alternative medicine as a non-mainstream practice used in place of conventional medicine [18]. CAM is further clarified by defining complementary, alternative and integrative approaches, as detailed in Table 1. Integrative health combines complementary and alternative therapies, while emphasising a broad-based approach to health and wellbeing that focuses on and treats the whole person rather than just an organ, inclusive of the many domains patients have identified as important to them (eg emotions, function, mental health, social, spiritual, community). This type of care has grown in recent years and is now being researched more frequently [19]. Indeed, what is considered to be CAM is in constant flux as therapies that are found to be safe and effective are adopted into conventional care [17]. A non-exhaustive list of potential CAM therapy is provided in Table 2, categorised by four distinct domains:

- Mind-body therapies
- Manipulative and body-based therapies
- Natural products
- Energy therapies.

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**Table 1. Definition of CAM** [17]

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<thead>
<tr>
<th>Complementary and Alternative Medicine (CAM)</th>
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<tr>
<td><strong>Complementary</strong></td>
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<tr>
<td>• Therapy used with conventional medicine</td>
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<td><strong>Alternative</strong></td>
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<tr>
<td>• Therapy used in place of conventional medicine</td>
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<tr>
<td><strong>Integrative</strong></td>
</tr>
<tr>
<td>• Combination of conventional medicine and complementary therapy</td>
</tr>
<tr>
<td>• Wellness and helping the “whole person”</td>
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</table>
LITERATURE REVIEW METHODOLOGY

English language articles were obtained via searches in Medline, Embase, and CINAHL using the target search words ‘haemophilia’ and ‘bleeding disorders’. These were then connected to additional search words related to CAM and specific therapy types, including meditation, Tai Chi, yoga, relaxation, distraction, cognitive reframing, neurolplasticity, humour, pet therapy, music therapy, art therapy, Buzzy Bee®, chiropractic, manipulation, massage, acupuncture, natural products, herbal products, essential oils, aromatherapy, Reiki, therapeutic touch and prayer. The searches were undertaken over a four-month period from June to September 2017. The only selection criteria were the use of CAM with PWH or bleeding disorders. Non-evidence-based articles, case reports and descriptions of therapy were considered alongside evidence-based articles and those involving randomised controlled trials; articles were also included regardless of the date of publication.

RESULTS

A total of 23 articles that described the use of CAM therapies with PWH or other bleeding disorders were identified, with publication dates ranging from 1971 to 2017.

Only ten articles were evidenced-based – these are detailed in Table 3, including a description of the articles’ aims and results. Only three articles were randomised controlled studies, involving hypnosis [19] and the use of distraction, including virtual reality [20,21]. Distraction was also addressed in a cross-sectional study [22]. One longitudinal study was identified using cognitive behavioural therapy [23]. A partial cross-over study undertaken in 1985 looked at relaxation exercises in PWH [24]. A pre- and post-test format was used in two studies, on the use of hypnosis and yoga [25,26]. A single blindered study and a nonrandomised descriptive study explored acupuncture use in PWH [27,28].

Table 4 outlines all non-evidence-based references that identified CAM usage in PWH. These include case reports, descriptions and a literature review. Case reports were noted in nine references: in mind-body therapies, including guided imagery [29,30] and hypnosis [31,32], manipulative and body-based modalities, on acupuncture in PWH [33-35], and in the energy therapy domain, including Reiki (described in blog format) and healing touch [37]. Three references used a descriptive study [38].

Table 2: The four domains of CAM, with examples of therapy

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<th>CAM DOMAIN</th>
<th>EXAMPLES OF THERAPY</th>
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| MIND-BODY           | • Meditation  
|                     | • Tai-Chi  
|                     | • Yoga  
|                     | • Relaxation  
|                     | • Hypnosis  
|                     | • Psychotherapy  
|                     | • Biofeedback  
|                     | • Cognitive reframing  |
| MANIPULATIVE & BODY-BASED | • Chiropractic  
|                     | • Massage  
|                     | • RICE (rest, ice, compression, elevation)  
|                     | • Acupuncture  
|                     | • Acupressure  
|                     | • Reflexology  
|                     | • Manipulation  |
| NATURAL PRODUCTS    | • Vitamins  
|                     | • Herbal products  
|                     | • Essential oils  
|                     | • Aromatherapy  |
| ENERGY THERAPIES    | • Reiki  
|                     | • Therapeutic touch  
|                     | • Prayer  |

Image: Although limited in number, studies show that people with haemophilia have found therapies including acupuncture, hypnosis, distraction and aromatherapy to be effective in helping to manage pain.
design to evaluate the use of prayer\textsuperscript{[4]}, massage\textsuperscript{[38]} and the use of essential oils\textsuperscript{[39]}. One literature review looked at the use of biofeedback in PWH\textsuperscript{[40]}.

**DISCUSSION**

As PWH are becoming more interested in using CAM for pain relief, it is important that healthcare providers avail themselves of relevant information so that they are better informed when presented with such requests. There is also an opportunity for healthcare professionals to consider alternative modes of pain management therapy that could be beneficial to PWH. Although CAM therapies can be viewed as having no scientific rationale, the literature review provides evidence indicating that both PWH and researchers are exploring these methods as alternatives to pain management. This reflects the more general trend in the literature towards exploring CAM with greater interest. Indeed, a more exhaustive review of the literature demonstrating the use of CAM in a variety of health-related pain issues, reveals a number of randomised controlled studies involving all four domains of CAM. These include the use of aromatherapy\textsuperscript{[41-43]} and Reiki\textsuperscript{[44,45]} in women’s health, yoga and mindfulness therapies in the treatment of back pain\textsuperscript{[46,47]}, Tai Chi and spiritual healing for neck pain\textsuperscript{[48,49]}, aromatherapy massage in the treatment of knee pain\textsuperscript{[50]}, the use of aromatherapy in burn patients\textsuperscript{[51,52]}, aromatherapy massage in female cancer patients\textsuperscript{[53]}, and aromatherapy and reflexology in rheumatoid arthritis\textsuperscript{[54]}.

The provision of pain management should involve a multimodal, personalised approach that best provides optimal benefits to the patient, while evaluating the risk/benefit ratio with each therapy discussed. When determining modes of pain therapy, it is important to consider the financial, cultural, and geographic issues that can affect decisions for treatment modalities, including CAM. To optimise pain management, it is imperative that providers ask the right questions in order to determine what treatment measures may provide a benefit to pain management in PWH. It is equally important to help guide PWH to qualified and licensed practitioners in specialised therapies, and to maintain ongoing communication between the PWH and the haemophilia care team during therapy. Determining any factor requirement needed to minimise potential bleeding risk that may arise with the chosen treatment option will always be a key consideration, and may involve additional factor dosing or adjustment of current prophylaxis regimens to coincide with pain treatment plans where the potential for bleeding risk may be higher.

The literature review suggests that there is ample opportunity for future research in all CAM domains, but perhaps particularly in the area of mind-body therapy domain, where neuroplasticity – or the potential for the brain to reorganise and create new neural pathways – plays a key role. Neuroplasticity processes are involved in chronic pain development occurring at the level of the brain cortex, peripheral nerves, and pain receptors. The important consequence of chronic pain neuroplastic changes is the reduced filtering ability of sensory neurons in the brain and spinal cord, resulting in the interpretation of painful stimuli which can potentially be exaggerated or misinterpreted\textsuperscript{[55]}. Therapies include, but are not limited to:

- Meditation and mindfulness techniques, where the mind is trained or induced into a level of consciousness involving a present-moment awareness through sensory, emotional, and/or cognitive events\textsuperscript{[56]}
- Cognitive behavioural therapy (CBT), where an experienced and trained therapist helps the person in pain reframe their painful experiences to change thoughts and behaviours to improve coping\textsuperscript{[17]}
- Biofeedback, where a trained practitioner guides the patient into relaxation using visual or auditory signals, with the intention of disruption the pain-anxiety-tension cycle, as well as decreasing the stimulation of the sympathetic nervous system\textsuperscript{[57]}
- Distraction, which involves redirection away from the pain experience using strategies that include, but are not limited to, playing video games, watching television, virtual reality, pet therapy, music and art

\[Image: There is scope for further research on the use and effectiveness of CAM for pain management in people with haemophilia. Mind-body therapies, involving techniques such as meditation, mindfulness, biofeedback and distraction, are an area of particular interest\]
therapy. Medical devices such as the Buzzy® use a form of distraction based on the gate control theory, where stimulating mechanoreceptors "shuts the gate" to the transmission of sharp pain through presynaptic inhibition. Several studies have shown this to have been particularly effective in children.\textsuperscript{[58-61]} Similarly, the Magic glove technique uses visualisation to 'numb' the relevant area from pain by guiding the patient to picture it being covered. This technique is frequently used most often in children undergoing venepunctures or IV insertions.\textsuperscript{[62]}

These and other therapies in the mind-body domain have the potential to help PWH manage their pain using nonpharmacological methods, which is arguably of particular importance given the current climate of opioid risk in some parts of the world.

Many of the articles identified during the literature review were completed between 1975 and 1992, and only five evidence-based articles involving the use of CAM in PWH were completed within the last ten years\textsuperscript{[20-23, 27].} Additionally, no articles based on a controlled study design were found within the natural products and energy therapy domains of CAM. This suggests that there is ample opportunity for future research in these areas. However, although the number of controlled studies using CAM is relatively low, all the references identified demonstrated some improvement in pain management within the respective technique described.

**CONCLUSION**

CAM options for pain management provide a wide variety of strategies that may provide benefits to PWH. Although there may be limited research with respect to CAM as a treatment option by PWH, consideration of its continued use should be explored if there is little or no bleeding risk. If there is limited risk but perceived benefit, it is suggested that continuation of the treatment option may be beneficial.

With the suggested shift away from pharmacologic approaches, it is increasingly important that healthcare professionals caring for PWH become educated in the multiple CAM treatment options available. Patients who defer systemic pain management or choose to augment their treatment plan may seek advice from the haemophilia care team to discuss alternative, nonpharmacological modes of pain management. For PWH, the goal of therapy should be to provide a combination of approaches that will best manage pain.

Well-designed research studies in all areas of CAM pain management options are needed for continued validation of these therapies in PWH. There are many opportunities for future research in this area of pain management.

**ACKNOWLEDGEMENTS**

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<th>ARTICLE (AUTHOR / YEAR /REFERENCE)</th>
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<td>Yoga</td>
<td>Beheshtipoor et al. 2005 26</td>
<td>Semi-experimental Pre-post-test design</td>
<td>Evaluate effects of yoga on quality of life in children and adolescents with haemophilia. Involved 27 boys, aged 8-16 years</td>
<td>• Significant differences were noted in quality of life dimensions, number of bleeding episodes and number of school absences • Yoga improved the physical, psychological and social domains</td>
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<td>Relaxation exercises</td>
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<td>Guided Imagery</td>
<td>Lichstein et al. 1985 24</td>
<td>Combined multiple baseline partial cross-over design</td>
<td>Effects of progressive and self-controlled relaxation on spontaneous bleeding and collateral symptoms. Seven PWH</td>
<td>• No strong evidence that the treatment affected bleeding frequency or perceived pain • Results failed to replicate previous findings and cast doubt on the stress theory of spontaneous bleeding • Further research is needed to clarify the role of psychological interventions for PWH</td>
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<td>Distraction</td>
<td>Elander et al. 2009 22</td>
<td>Cross-sectional study</td>
<td>Evaluation of influence of active pain coping, passive adherence coping and negative thoughts about pain, activity engagement and pain willingness on physical and mental aspects of quality of life. 209 men with haemophilia A or B.</td>
<td>• Pain intensity had the main influence on physical quality of life; negative thoughts had the main influence on mental quality of life • Activity engagement and pain willingness had small but significant influences on physical and mental quality of life • Pain willingness mediated the influence of pain intensity on physical quality of life and activity engagement • Pain willingness mediated the influence of negative thoughts on mental quality of life • There was no evidence that active pain coping influenced quality of life • Findings suggest that quality of life for PWH could potentially be improved by interventions to increase pain acceptance and reduce negative thoughts about pain</td>
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<td></td>
<td>Elander et al. 2011 20</td>
<td>Randomised controlled trial</td>
<td>Two-phase motivational-volitional model of readiness to self-manage pain, including the personal experiences of PWH. 164 PWH with arthritic pain</td>
<td>• Findings are consistent with a two-phase, motivational-volitional model of pain self-management, and provide the first insights in our knowledge of readiness to self-manage pain in PWH • Low-intensity interventions in DVD format can improve the motivational impact of written information and could be used to help prepare people with chronic pain for more intensive self-management interventions</td>
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<td>Dunn et al. 2017 21</td>
<td>Single centre randomised 2:1 pilot study</td>
<td>Evaluating the difference in procedure time of IV insertion with use of virtual reality in children with haemophilia. 25 children with haemophilia, median age 12.2 years</td>
<td>• Children and their parents viewed the virtual reality (VR) method as a positive distraction • No adverse disruption in clinic flow • No significant difference in group allocation between sex, age, type of haemophilia, haemophilia severity or use of prophylaxis • Median VR procedure time was ten minutes • No difference in scores between groups in terms of nervousness prior to IV, or impact of distraction technique on level of engagement, impact on pain, anxiety or likability. In the VR cohort, the median scores for ease of use and desire to use VR for future procedures was highly positive for patients, nurses and parents</td>
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| Cognitive reframing               | Elander et al. 2013 23            | Longitudinal study | Low-intensity psycho-educational program to promote readiness to self-manage chronic joint pain. 101 male PWH | • Reduced pain intensity predicted better physical quality of life, regardless of age, haemophilia severity, baseline pain intensity and baseline physical quality of life.  
• Lower baseline passive coping and changed (increased) pain acceptance predicted better mental quality of life, regardless of age, haemophilia severity and baseline mental quality of life.  
• Increased activity engagement predicted better mental quality of life.  
• Reduced negative thoughts predicted better mental quality of life.  
• Active pain coping did not predict physical or mental QoL. |
| Hypnosis                          | Swirsky-Sacchetti, Margolis 1986 25 | Random design Pre-post-test design | Study of comprehensive self-hypnosis training to decrease stress and assess amount of clotting factor usage for bleeding in persons trained in hypnosis vs controls. 30 severe PWH randomly assigned. | • The general level of distress was significantly reduced in the treatment group.  
• Treatment significantly reduced the amount of factor concentrate used to control bleeding in comparison to controls. |
| LaBaw                              | 1975 19                           | Randomised controlled study Randomised to hypnosis therapy or control group. 20 PWH participated | Statistical analysis of the data confirmed the clinical observation of a greater improvement among patients in the experimental group in reduction of transfused products. |
| MANIPULATIVE AND BODY-BASED THERAPIES |                                    |                     |                   |                   |
| Acupuncture                       | Wålmy et al. 2006 35              | Single blinded study | PWH with joint pain; non-pain side used as control. 12 PWH participated | • Reduction in pain in 10 of 12 PWH after acupuncture treatments.  
• No procedural bleeding noted.  
• Pain reduced from 6.8 to 5/10 per visual analogue scale. |
|                                  | Lambing et al 2012 27             | Non-randomised, descriptive | (i) Identify effects of acupuncture use in PWH who experience persistent joint pain due to haemarthrosis; (ii) document no reported increased bleeding risk as a result of acupuncture use. Six US subjects received prophylaxis factor prior to acupuncture; three subjects from India received no factor prior to treatments. | • Seven out of nine PWH reported an improvement in pain scores and quality of life.  
• No bleeding or bruising was reported by any subjects, regardless of whether or not they received factor pre-treatment.  
• Acupuncture therapy can be a safe additional modality for pain management in PWH, although larger randomised studies are needed. |
| NATURAL PRODUCTS: NONE             | ENERGY THERAPY: NONE              |                     |                   |                   |
Table 4: Non-evidenced-based articles from literature review of the use of CAM for pain in people with haemophilia

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| Relaxation exercises                | Varni 1981 29                       | Case report  | Training in use of progressive muscle relaxation, meditative breathing and guided imagery. Two PWH with chronic arthritic pain | • Imagery training resulted in clinical reduction in arthritic pain  
• Subjects were able to demonstrate thermal control of their joints  
• An increase in thermal heat at the joint resulted in decreased pain perception |
| Guided imagery                      | Varni 1981 30                       | Case report  | Training in self-regulation techniques including progressive muscle relaxation exercises, meditative breathing and guided imagery.  
Three PWH with chronic arthritic pain | • Clinically significant reductions in arthritic pain perception for all three PWH were noted, with maintenance demonstrated at 12, 14 and 7 months, respectively  
• Overall improvements in pain, sleep and mobility, and decrease in analgesic use  
• Physiological assessment of surface skin temperature at the arthritic joints |
| Biofeedback                         | Bradley et al. 1984 40              | Literature review | Mind body therapies used in PWH with rheumatoid arthritis | Review of studies by Varni (references 29 and 30), LaBaw (reference 19), and Swirsky-Sacchetti and Margolis (reference 25) |
| Hypnosis                            | Newman 1971 31                      | Case report  | Hypnosis training in a 43 year-old female bleeding patient for tooth extraction | • No bleeding reported during surgical extraction |
|                                     | LaBaw 1992 32                       | Case report  | Education of PWH on self-hypnosis. Two case reports | • Subject was able to control bleeding and continue family vacation  
• Five-year-old boy using hypnosis >10 years; self-reported reduction of factor infusions needed by 50%  
• 19-year-old able to reduce hospitalisations from bleeding episodes, prior to succumbing to AIDS; able to use hypnosis to avoid terminal hospitalisation |
| **MANIPULATIVE AND BODY-BASED THERAPIES** |                                     |              |                    |                  |
| Massage therapy                     | Beyer et al. 2010 38                | Descriptive  | Massage therapy in PWH | • Treatment and preventive strategies include RICE (rest, ice, compression and elevation), protected mobilisation, stretching and strengthening exercises, manual therapy (articular, neural and soft tissue mobilisation and massage), and correction of movement dysfunction, functional rehabilitation and electrotherapeutic interventions  
• Improved circulation and range of motion noted |
| Acupuncture                         | Koh 1981 33                         | Case report  | Patient #1: 40-year-old PWH with left shoulder osteoarthritis  
Patient #2: 36-year-old PWH with right knee and ankle pain | • Patient #1 free of pain for more than five months post-treatments  
• Patient #2: reduction of oral pain medication  
• Both patients tolerated treatments well with no complications  
• PWH should receive factor treatment prior to acupuncture therapy |
| NON-PHARMACOLOGIC TREATMENT OPTIONS | ARTICLE (AUTHOR / YEAR /REFERENCE) | ARTICLE TYPE | INTERVENTIONS/AIMS | RESULTS/OUTCOMES |
|---------------------------------|-------------------------------------|--------------|--------------------|-----------------
| | Rosted, Jorgenson 2002 34 | Case report | 38-year-old PWH who received three elbow treatments and five knee treatments | • Patient reported a reduction in pain and opioid usage  
• Repeat acupuncture every three months as needed provided continued improvement |
| | Martini et al. 2014 28 | Case report | 43-year-old female with type III von Willebrand's disease and chronic migraines | • Improvement in migraine pain without bleeding or bruising  
• No adverse effects of somatic needling noted  
• No auricular cryostimulation reported  
• No bleeding reported |
| NATURAL PRODUCTS | Aromatherapy and essential oils | Vicol 2013 39 | Descriptive | Aromatherapy to manage side-effects of HIV | • Under study for potential benefit in treating hepatitis C and haemophilia |
| ENERGY THERAPY | Reiki | HoG blog 2012 36 | Case report (personal) | Use of Reiki to help with back pain following car accident | • First session yielded noticeable pain relief and muscle relaxation.  
• Subsequent sessions continued to relieve pain and increased time between muscle spasms |
| | Therapeutic touch | Krug et al. 2013 37 | Case report (abstract) | PWH with hepatitis C receiving therapeutic touch | • 30-40% relief in fatigue and pain.  
• Normalisation of thyroid function |
| | Prayer | Witkop et al. 2012 4 | Description | • Identify language used by PWH to describe pain  
• Describe pharmacological and nonpharmacological methods of pain management used  
• Determine perceived effectiveness of pain management  
• Determine which healthcare practitioner manages pain in PWH  
• 764 PWH self-reported results | • The use of prayer to manage acute pain (28% N=189;) and chronic pain (29% N=170), and faith for acute pain (21%) N=137, and chronic pain (22%) N=130 |
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