

Narrative Review

Pain and Opioid Use in Cancer Survivors: A Practical Guide to Account for Perceived Injustice

Jo Nijs, PhD^{1,3}, Eva Roose, MSc^{1,4}, Astrid Lahousse, MSc^{1,4,5}, Kenza Mostaqim, MSc¹, Iris Reynebeau, MSc¹, Marijke De Couck, PhD^{1,6,7}, David Beckwée, PhD⁴, Eva Huysmans, MSc^{1,2,5,7}, Rinske Bults, MSc^{1,8}, Paul van Wilgen, PhD^{1,8}, and Laurence Leysen, PhD^{1,4}

From: ¹Pain in Motion International Research Group (PAIN), Department of Physiotherapy, Human Physiology and Anatomy, Vrije Universiteit Brussels, Belgium; ²Chronic Pain Rehabilitation, Department of Physical Medicine and Physiotherapy, University Hospital Brussels, Belgium; ³Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden; ⁴Rehabilitation Research Department, Department of Physiotherapy, Human Physiology and Anatomy, Vrije Universiteit Brussels, Belgium; ⁵Research Foundation – Flanders (FWO), Brussels, Belgium; ⁶Odisee University College, Campus Aalst & Brussels, Belgium; ⁷Department of Public Health (GEWE), Vrije Universiteit Brussel, Brussels, Belgium; ⁸Transcare Pain Transdisciplinary Pain Treatment Center, Groningen, the Netherlands

Address Correspondence:

Jo Nijs, PhD
Vrije Universiteit Brussel, KIMA-PAIN,
Laarbeeklaan 103, BE-1090 Brussels,
Belgium
E-mail: Jo.Nijs@vub.be

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Background: The presence of pain decreases survival rates in cancer. Pain management in clinical settings is often suboptimal and secondary to other cancer-related treatments, leaving many people undertreated. Opioid use is associated with side effects and decreased survival rate in cancer patients. Hence, there is an urgent need for considering factors such as perceived injustice that sustain post-cancer pain and trigger a behavioral pattern associated with opioid use. Injustice beliefs represent a maladaptive pattern of cognitive appraisal that may be a salient target for improving pain-related coping in these patients. Perceived injustice is associated with increased opioid prescription and prospectively predicted opioid use at 1-year follow-up, urging the need for targeted interventions to diminish perceived injustice.

Objectives: Explain the importance of screening for perceived injustice in patients with pain following cancer treatment, its potential relevance for opioid abuse, and its potential impact on the management of pain following cancer. Also, prove clinicians with a clinical guide for an approach comprising of modified pain neuroscience education, motivational interviewing, and acceptance-based interventions to account for perceived injustice in patients having pain following cancer.

Study Design: A narrative review, perspective and treatment manual

Setting: Several universities, a university of applied science department, a university hospital, and a private clinic (i.e., transdisciplinary pain treatment center).

Methods: Patients were cancer survivors with pain. Intervention included modified pain neuroscience education, motivational interviewing, and acceptance-based interventions. Measurements were taken through the Injustice Experience Questionnaire (IEQ).

Results: The IEQ can be used to assess perceived injustice in a valid way. Education about pain, including discussing perceived injustice, should be the first part of the management of pain in cancer survivors. In order to obtain the often-required behavioural change towards a more adaptive lifestyle, motivational interviewing can be used. To thoroughly tackle perceived injustice in patients having pain following cancer, special emphasis should be given to the individual reasons patients identify for experiencing (continued) pain and related symptoms. Pain acceptance should also be thoroughly addressed.

Limitations: Clinical trials exploring the benefits, including cost-effectiveness, of such a multimodal approach in patients with pain following cancer treatment are needed.

Conclusions: In light of its potential relevance for opioid abuse and potential impact on conservative management strategies, clinicians are advised to screen for perceived injustice in patients with pain following cancer treatment. Therapeutic targeting of perceived injustice can be done through an approach comprising of modified pain neuroscience education, motivational interviewing, and acceptance-based interventions.

Key words: Anger, cancer, counselling, education, medication use, motivational interviewing, neuroscience education, opioid, perceived injustice, rehabilitation, survivor

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In the survival stage following cancer, pain is one of the primary, most disabling, and prevalent symptoms (1). Chronic severe pain, which interferes with functioning, is seen in approximately 5-10% of cancer survivors and even reaches up to 40% in the early post-treatment period (2). Currently, pharmacological treatment is the standard treatment approach for cancer-related pain (3). Pain management in clinical settings is often suboptimal and secondary to other cancer-related treatments, leaving many people undertreated (4). This is worrying, especially because available data indicate that the presence of pain decreases survival rates in cancer (5). Since opioid use is associated with side effects, such as constipation, respiratory depression, and addiction potential (6) as well as with decreased survival rate in cancer patients (7), opioids are not a valuable solution to treat cancer pain. Hence, non-pharmacological management should be the cornerstone of post-cancer pain treatment (8), which is in line with the biopsychosocial nature of the post-cancer pain problem (9, 10) and best-evidence treatment for non-cancer pain (11).

Of importance in the development of non-pharmacological treatment, recent work indicates that perceived injustice contributes to unravelling the complex biopsychosocial puzzle of chronic pain following cancer (12). Perceived injustice has been conceptualized as a multidimensional appraisal process characterized by a tendency to interpret one's losses as severe and irreparable, to attribute blame to others for one's suffering, and to experience a sense of unfairness (13) (eg, someone who never smoked yet was diagnosed with lung cancer). Perceived injustice is related to feelings of helplessness, due to beliefs about the uncontrollable nature of the source of injustice or the predominant role of others in perpetuating a health-related issue (14). Perceived injustice inherently presumes a discrepancy between expected and actual outcomes, which may lead to feelings of anger, frustration, or other forms of emotional distress (14). These feelings in turn may lead to an increased pain sensitivity; anger is associated with endogenous opioid dysfunction in response to painful stimuli, increased muscle tension, and systolic blood pressure (15,16). Besides that, perceived injustice incorporates a strong aspect of social comparison that may foster social conflict and greater distress (eg, the nature of a stressor is not only negative, but also unjust in comparison to the experiences of others) (14). A recent systematic review found strong evidence for an association between perceived injustice and worse pain-related outcomes,

such as higher pain intensity, more disability, and worse mental health (17). The presence of perceived injustice was also found to be related with reduced quality of life and social functioning (17). Indeed, patients that construe their health challenges with beliefs of injustice can experience a higher self-reported pain intensity, maladaptive pain beliefs, prolonged and problematic recovery, poorer treatment outcomes, grave disability, more severe symptoms of depression, fatigue and sleep disturbances, a reduced likelihood of return to work at 1-year follow-up, impaired psychological functioning, as well as poor physical health (13, 18). Taken together, injustice beliefs represent a maladaptive pattern of cognitive appraisal that may be a salient target for improving pain-related coping (14).

In a study of 110 breast cancer survivors, higher perceived injustice scores were related to lower quality of life. Perceived injustice rather than pain catastrophizing mediated the relation between pain and quality of life (12). The relative salience of perceived injustice, as mediator of quality of life among breast cancer survivors, underscores the fact that perceived injustice is not only understudied, but also underappreciated and undertreated in the breast cancer survivor population (12). Therefore, it may be important to incorporate the recognition and reduction of perceived injustice as a treatment strategy in the rehabilitation of breast cancer survivors. Current approaches to the management of pain following cancer do not include techniques specifically designed to reduce perceptions of injustice; therefore, we explain here the importance of screening for perceived injustice in patients with pain following cancer treatment, its potential relevance for opioid abuse, and its potential impact on the management of pain following cancer. Finally, an approach comprising of modified pain neuroscience education, motivational interviewing, and acceptance-based interventions is proposed to account for perceived injustice in patients having pain following cancer.

The Importance of Perceived Injustice in relation to Pain following Cancer: Preventing Opioid Crisis among Cancer Survivors

Preclinical studies suggest that opioids may have an impact upon the core features of the cancer process. Opioids have detrimental effects on immune function (including natural killer cell numbers and cytotoxicity) in cancer (19,20), the μ -opioid receptor promotes tumor initiation in hepatocellular carcinoma (21), and the δ opioid receptor is highly expressed in breast cancer and is

closely related to its progression (22). The World Health Organization recommends opiate analgesics for the management of cancer pain (23-25), but, in the survivorship setting, its use is often discouraged due to the long-term side effects, such as the development of opiate-induced hyperalgesia, as well as addiction and abuse risks (26). More specifically, long-term opioid therapy might cause opioid-induced hyperalgesia, a state of hypersensitivity to painful stimuli associated with opioid therapy, resulting in exacerbation of pain sensation rather than relief of pain (27). Besides that, the use of opioids may also result in daytime fatigue, drowsiness, and napping, which in turn contributes to the aggravation of the sleep disruption often seen in cancer patients (28,29). Additionally, there is growing evidence that opioids may contribute to central sleep apnea, which further enhances daytime symptoms and hypoxia (29).

Safe and appropriate pain management, including prevention of opioid misuse or abuse, is an important survivorship issue (30). Indeed, cancer is associated with current opioid use (31). Patients undergoing oncologic surgery are at risk for persistent postoperative opioid use (32). Opioid use has also been seen to contribute to central nervous system symptoms among cancer patients (33). Reflective of the risks of long-term adverse effects associated with opioids (eg, loss of pain-relieving effects or analgesic tolerance, opioid-induced hyperalgesia, and opioid addiction (34)) and the opioid abuse epidemic affecting the general population (35,36), the potential for misuse or abuse exists in both those with cancer and cancer survivors (37,38). The vast majority (77%) of cancer patients improperly and unsafely store, use, or dispose of opioids (39). This highlights the need to investigate the impact of patient education on such practices (39).

In addition to its clinical importance, as explained in the introduction section, perceived injustice is also associated with increased opioid prescription (40) and prospectively predicted opioid use at 1-year follow-up (41), urging the need for targeted interventions to diminish perceived injustice. The increased opioid use might be related to propensity in individuals with high levels of perceived injustice to use pain behavior to emphasize the magnitude of their suffering (13,40) (Fig. 1). Indeed, research has demonstrated that clinicians are more likely to prescribe opioids to patients who display more pain behavior (42) and that pain behavior emerged as a mediator of the relationship between perceived injustice and opioid prescription (40). Individuals who view their pain in terms of injustice may display more pain behavior as a means of com-

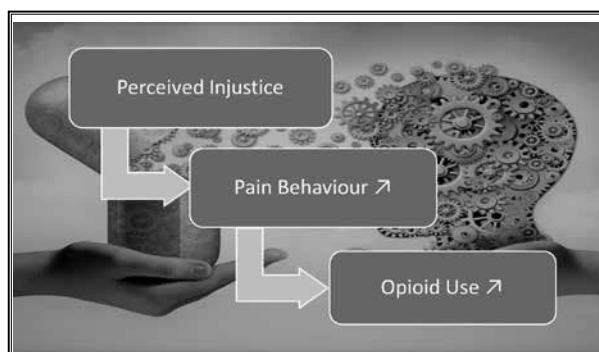


Fig. 1: *The impact of perceived injustice on opioid use.*

municating the intensity of their suffering and losses, which inadvertently increases the likelihood of being prescribed opioids (40).

Assessing Perceived Injustice in Cancer Survivors

Thirty percent of breast cancer survivors who present with pain, also present with perceived injustice (12). Hence, the first step for clinicians is screening for perceived injustice among their cancer survivors. The Injustice Experience Questionnaire (IEQ) can be used to assess perceived injustice (43). The scores obtained using the IEQ are valid (41,44-46). Clinically relevant perceived injustice is present when a patient scores 30 or higher on the IEQ (43); however, due to its inability to identify patients in terms of follow-up employment status, IEQ scores of 19 or higher have been suggested as cut-off, as well (41). In addition to its total score, the IEQ also generates 2 subscale scores, with 14 as cut-off for the blame subscale, and 16 for the severity/irreparability subscale (43).

In addition to the IEQ, the Trait Injustice Experience Questionnaire (T-IEQ), a 12-item scale that measures the extent to which individuals experience injustice in relation to adverse life experiences (47), was recently developed. Its content was drawn from the original IEQ and adapted for relevance to a non-injury context (47), which may be of significance to the cancer survivor population, but studies exploring the use of the T-IEQ in cancer survivors are currently lacking.

Therapeutic Targeting of Perceived Injustice in Cancer Survivors

Perceived injustice-targeted pain neuroscience education

Cancer patients indicate that they have insufficient

knowledge regarding pain, during or after cancer, what the possibilities of pain relief are, and how they can access support when needed (48,49). When comparing pain knowledge between cancer survivors, healthy controls, and caregivers, cancer survivors had lower pain knowledge than caregivers and even healthy controls (50). Hence, the education about pain should be the first part of the management of pain in cancer survivors. Education about pain is underused in the field of oncology and non-existent in the survivorship phase (51). The content of the used education is variable and poorly established (51), with most of the educational interventions for cancer survivors being restricted to more biomedical pain management instructions (eg, use of analgesics) (51). The latter is problematic as the biomedical model falls short in explaining persistent pain following cancer; therefore, current patient-based educational interventions emphasize a biopsychosocial framework (52). This includes discussing perceived injustice, if present, with the patient. When doing so, clinicians are advised not to use wordings like 'perceived injustice,' as they might trigger resistance, especially in those cancer survivors reluctant of a biopsychosocial understanding of their problem. Instead, wordings such as 'unfair' and 'blame' are more appropriate. Examples of questions clinicians can ask their patients are: "Do you feel it's unfair that you still suffer from pain, especially after all you've been through?" and "Who or what do you blame for your pain."

Despite the fact that specific treatment plans for perceived injustice are not yet proven (53), literature suggests the use of cognitive-behavioural interventions, pain acceptance (13), and educational interventions comprised of elements of reassurance and encouragement towards activity re-engagement (54). One such intervention is pain neuroscience education (PNE). The use of PNE entails a dramatic shift in educating patients with persistent pain following cancer (55). Rather than purely focusing on the biomedical characteristics of pain following cancer (e.g., tissue damage due to past breast cancer treatment, myofascial trigger points), PNE implies teaching patients about the underlying biopsychosocial mechanisms of persistent pain in cancer survivors and provides reassurance and encouragement towards activity re-engagement. Therefore, PNE is a cognitive behavioural intervention which includes educating patients that pain is an output product of the brain resulting from input from multiple central and peripheral nervous system processes leading to the perception of threat (52).

In the treatment phase of cancer, pain is considered to be part of the suffering, but after this process it is difficult for patients to understand and accept that they are 'cured' yet continue to suffer from pain. PNE addresses this by explaining complex pain mechanisms known to be of importance in pain following cancer, such as malfunctioning of the endogenous analgesic system (55) and pain memories (56), using metaphors. A cardinal feature is to individually tailor content to the patient's maladaptive beliefs regarding pain. The PNE intervention presented here is specifically aimed at targeting perceived injustice next to other maladaptive cognitive and emotional factors. During a first PNE session, perceived injustice can be briefly included as a sustaining factor for pain and central nervous system sensitization. This can serve as a first step for patients in accepting their condition and associated suffering and should ease patients into talking about perceived injustice during the next session. To facilitate (deep) learning, the information should be presented to the cancer survivors verbally (explanation by the therapist) and visually (summaries, pictures, metaphors, and diagrams on computer screen, whiteboard, and/or paper). Also, it is recommended to supplement live therapy sessions with written material to establish deep learning (55), especially because of the potential occurrence of "chemo-brain" in cancer survivors (58). The discussed topics during the sessions can include medication use. In case patients use opioids, possible side effects can be discussed. In case patients experience side effects, the pros and cons of opioid use can be discussed and explanation regarding opioid-induced hyperalgesia and related addiction risk can be provided. Depending the outcome of balancing the pros and cons, they can be advised to explore the option of withdrawal with their treating physician. This way, medication withdrawal can become a treatment goal.

In non-cancer pain populations, PNE is welcomed very positively (25,59) and has proven to be effective in decreasing pain intensity, increasing physical performance, and improving quality of life, as well as pain coping strategies (25,59-66). Taken together and as illustrated in Figure 2, PNE appears to be an appropriate intervention for addressing the consequences of perceived injustice.

The use of PNE in cancer survivors suffering from persistent pain has been proposed repeatedly (10, 67). We developed a practical guide for clinicians to explain pain following cancer (55). The potential of PNE in breast cancer survivors has been explored in an

observational, uncontrolled study comparing pre- to post-PNE status in 30 patients suffering from persistent pain following cancer (63% breast cancer survivors) (68). The study demonstrated that the cancer survivors experienced a statistically significant decrease in pain and improved quality of life (medium effect sizes) 2 weeks after a single session of PNE (68). Rumination ($P = 0.002$, $r = -0.39$) and helplessness ($P < 0.001$, $r = -0.48$), key aspects inherent to perceived injustice (14), also improved following PNE in breast cancer survivors (medium effect sizes), underscoring the idea that PNE is appropriate for addressing perceived injustice in cancer survivors. Finally, given its pain-relieving effects (60,69), its focus on active pain coping strategies (69), and its health care expenditure reducing effects (70,71), PNE might lead to a decrease in opioid prescription and use among cancer survivors. Breast cancer survivors may express frustration and confusion as they experience a shift away from opioid use as the primary pain management strategy. Therefore, it is of utmost importance that the clinician carefully clarifies the rationale for changing the treatment plan from one in which the primary focus is set on opioids with escalation-upon-demand, to one of multimodal therapies.

Motivational interviewing

Still, PNE in itself is unlikely to suffice for thoroughly addressing perceived injustice in patients having pain following cancer. Therefore, and in order to obtain the often-required behavioural change towards a more adaptive lifestyle, motivational interviewing is used as the communication process throughout PNE (72). Figure 3 illustrates the key components of strategies that target perceived injustice as a sustaining factor for pain and other post-cancer-related symptoms. Motivational interviewing is a direct, collaborative, patient-centered communication approach for eliciting and enhancing motivation for behavior change by helping clients to resolve ambivalence and uncertainty (73,74). Motivational interviewing, as well as PNE, adheres to guidelines for patient-centered care (75), including offering individualized treatment, continuous communication (verbal and non-verbal), education during all aspects of treatment, and working with patient-defined goals in treatment where the patient is supported and empowered by a confident therapist, with social skills, giving them specific knowledge (76). A practical guide, including a script for combining motivational interviewing with PNE (72), is available and the script has been translated in multiple languages (<http://www.paininmotion.be/education/tools-for-clinical-practice>).

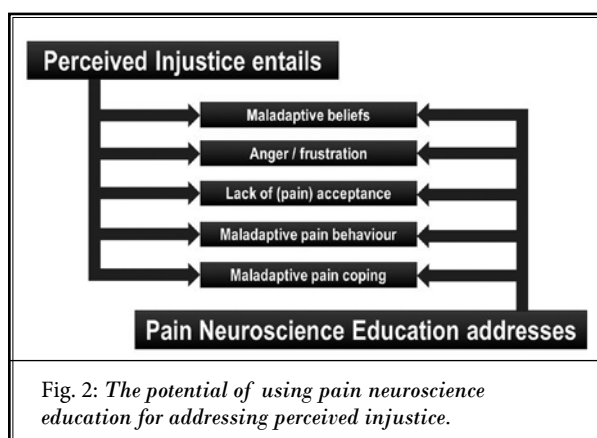


Fig. 2: The potential of using pain neuroscience education for addressing perceived injustice.

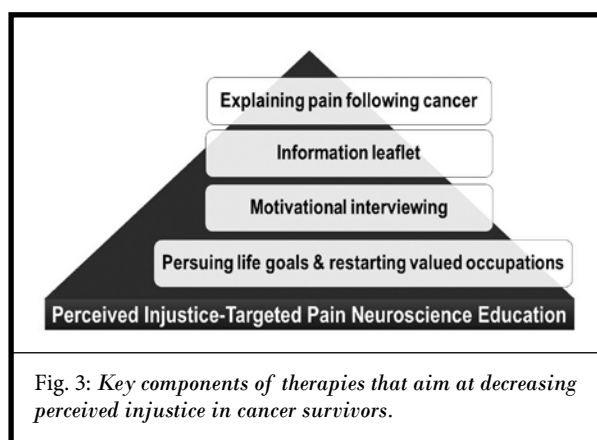


Fig. 3: Key components of therapies that aim at decreasing perceived injustice in cancer survivors.

Motivational interviewing implies that the therapist is supportive, empathetic, positive and hopeful. It also relies on the therapeutic alliance to assist in changing certain health behaviors based on the patients' internal thoughts, such as perceived injustice, decisions, and motivation. Examples include:

- "I can understand that you expect me to have a quick solution for your pain experience, especially after the long cancer treatment period"
- "It's up to you to decide if, and when, you are ready to change how you are dealing with the pain, fatigue, and other problems you are dealing with, but please know that we are available to help you."

Cancer survivors are more willing to discuss changing behaviours, thoughts, or habits when asked, than when being lectured or told to change. Integrating PNE implies that the therapist asks the cancer survivor for permission to talk about an understanding of pain neuroscience. Examples of asking permission are (modified from (72)):

- “Your oncologist said she could not entirely relate your pain to the damage caused by your treatment. Are you willing to look at it from a more comprehensive perspective?”
- “You told me that you aim at returning to long-distance running, but currently even a gentle walk is triggering pain. Do you mind if we talk about why such low-intensity activity is currently triggering more pain and search for a solution together?”

Motivational interviewing also aims to strengthen personal commitment by respecting the individual's autonomy and assists them in reaching a specific goal by exploring personal intentions or reasons for change (73,74). For example, patients can be asked whether they prefer investing energy into fighting the unfairness/injustice –knowing that this will aggravate their pain– or into fun leisure time activities that may relieve pain. This goal setting towards valued life goals should be done with a very broad focus, possibly also including social goals and certainly not restricted to just physical activity. The patient defines their own treatment goals. Examples include:

- “Your pain is currently controlling your life – the pain is telling you what to do and what not to do and you rely on short-term pain relief. How do you feel about switching the focus towards long-term solutions, including targeting a return to fun leisure time activities that you can chose yourself?”
- “Everyone who's ever changed from short-term pain relief to long-term solutions starts right where you are now; they start by seeing the reasons where they might want to change towards more sustainable ways of dealing with your post-cancer [insert anatomical region if appropriate] pain.”

To thoroughly tackle perceived injustice in patients having pain following cancer, special emphasis should be given to the individual reasons patients identify for experiencing (continued) pain and related symptoms. In addition, pain acceptance (Fig. 2) should be thoroughly addressed. Perceptions of injustice often lead to individuals being “stuck” in a struggle to control pain, which lets them resort to passive coping mechanisms, such as medication use, which do not require them to actively cope with their pain and pain-related thoughts (77). Individuals with high perceived injustice may intentionally disengage in meaningful activities and constantly attempt to reduce or avoid pain to seek adequate retribution for losses, as this disability might

represent the only ‘power’ that an individual possesses in efforts to communicate the extent of losses sustained (78). Therefore, motivational interviewing aims to encourage patients with pain following cancer to pursue life goals again and restart valued occupations while experiencing pain, by eliminating the feeling of wanting to control or avoid pain (13,79). Pain acceptance will be addressed by broadening their understanding of the pain problem, including discussing the possible pain aggravating role of anger and frustration:

“We have now addressed several factors that contribute to your pain experience, including depressive mood and lack of physical activity. We also discussed that it is understandable for you to feel a bit frustrated about your inability to immediately return to your level of daily functioning from before the cancer was diagnosed. Do you think that feeling frustrated impacts upon your pain experience?”

The presence of perceived injustice implies that the patient with pain following cancer struggles with acceptance. Addressing the lack of acceptance is key to allow patients to focus on (long-term) self-defined goals. As discussed in the section on perceived injustice-targeted PNE, explaining the role of pain in cancer survivors and the sustaining factors relevant for the individual patient is a first step in the acceptance process. Motivational interviewing will be key for the next step: patients can be taught to address their anger and frustration (i.e., what they consider unfair and who/what they blame) as a stressor, for instance by using a cognitive approach, such as the Eliminate–Change–Accept (ECA) method. In this approach, patients reflect on the 3 options (eliminate, change, accept) for dealing with their anger / frustration (Table 1). Depending on the individual patient and how they responded to the PNE and ECA method for improving acceptance, specific strategies for achieving acceptance such as acceptance and commitment therapy can be indicated.

CONCLUSIONS

Recent work indicates that perceived injustice contributes to unravelling the complex biopsychosocial puzzle of chronic pain following cancer (12). Injustice beliefs represent a maladaptive pattern of cognitive appraisal that may be a salient target for improving pain-related coping in those who survived cancer, yet continue to struggle with feelings of anger and frustration (14). In light of its potential relevance for opioid abuse and potential impact on conservative management strategies, clinicians are advised to screen

Table 1: *The Eliminate–Change–Accept (ECA) method as a cognitive approach for decreasing patient’s anger and frustration (i.e., what they consider unfair and who/what they blame) that is inherent to perceived injustice.*

	Eliminate	Change	Accept
Strategy	The patient is asked to identify the reason(s) of her/his anger and/or frustration(s). Next, the patient is invited to explore the possibility of deleting those reasons from her/his life.	The patient is asked to consider the option of changing the reason(s) of her/his anger and/or frustration(s).	In case eliminating or changing the source of anger / frustration is not really an option, there’s nothing left besides accepting the situation. Teaching the patient to apply relaxation techniques to handle the stress triggered by the source of anger / frustration often helps with acceptance. Also, this entire process of reflecting on the 3 options (eliminate – change – accept) for dealing with their anger / frustration is helpful in the acceptance process. Simply knowing that there’s nothing else they can do about it, and that they reflected thoroughly on all possible options, can help a lot.
Example	A patient is angry with the surgeon who treated her for her breast cancer. Will it help her if she never visits the surgeon’s hospital again? No, she says, because she is very happy with the care provided by the oncologist and nurses of that hospital, and she doesn’t want to lose them. The net result is that eliminating the surgeon from her life is not an option. This leaves her with 2 more options (changing or accepting the surgeon).	Is the patient able and willing to change the surgeon? She could sue the surgeon, but she’s not willing to do that. She says the surgeon didn’t make a professional mistake; he only did a poor job in informing her about the possible side effects of the surgical intervention. That’s why she is so angry with him. Perhaps contacting him to discuss this in more detail would be helpful? She will think about it.	If the patient is not willing to change hospitals, sue the surgeon, or discuss her issues during a face-to-face meeting with the surgeon, only 1 option remains. She needs to accept the situation. That does not mean that she’s left alone in her misery. On the contrary, the therapist is available to support her with accepting the situation as it is. Thoroughly discussing all options is crucial for making the patient aware of the situation, and should aid them in accepting the situation. Next, the therapist offers to teach relaxation skills to handle the stress that comes along with it. This can include training the patient in practicing relaxation skills before, during, and following her next appointment in the surgeon’s hospital.

for perceived injustice in patients with pain following cancer treatment. Therapeutic targeting of perceived injustice can be done through an approach comprising of modified pain neuroscience education, motivational

interviewing, and acceptance-based interventions. Clinical trials exploring the benefits, including cost-effectiveness, of such a multimodal approach in patients with pain following cancer treatment are needed.

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