

TEST (Trivent Ethics in Science and Technology Imprint)
Heading Towards Humans Again: Aspects of
Bioethics in the New Age of Science
Ed. Miroslav Radenković
Available online at <http://trivent-publishing.eu>



Ethical Issues Regarding Chronic Pain From the Perspective of a Clinical Pharmacologist

Katarina Savić Vujović,¹ Miroslav Radenković,¹ Branislava Medić,¹
Slađana Mihajlović,² Sonja Vučković,¹ Nevena Divac,¹
Radan Stojanović,¹ Dragana Srebro,¹ Miloš Basailović,¹ Milica Prostran¹

¹ Department of pharmacology, clinical pharmacology and toxicology,
Faculty of Medicine, University of Belgrade, Belgrade, Serbia

² Ob/Gyn Hospital, University Clinical Centar "Dr Dragisa Misovic Dedinje",
Belgrade Serbia

DOI: 10.22618/TP.AEBIO.20214.231007



This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC-BY-NC-ND 4.0) license, which permits others to copy or share the article, provided original work is properly cited and that this is not done for commercial purposes. Users may not remix, transform, or build upon the material and may not distribute the modified material (<http://creativecommons.org/licenses/by-nc/4.0/>)

ETHICAL ISSUES REGARDING CHRONIC PAIN FROM THE PERSPECTIVE OF A CLINICAL PHARMACOLOGIST

Katarina Savić Vujović,¹ Miroslav Radenković,¹ Branislava Medić,¹
Slađana Mihajlović,² Sonja Vučković,¹ Nevena Divac,¹
Radan Stojanović,¹ Dragana Srebro,¹ Miloš Basailović,¹ Milica Prostran¹

INTRODUCTION

Pain is the most common symptom of a disease. It is defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”³ Qualified specialists in the field of pain are responsible for adequate and successful pain treatment as an ethical imperative and obligation. Acute and chronic pain are different clinical entities. Acute pain is pain that appears suddenly, can be severe, but lasts a relatively short period of time. Acute pain is usually induced by inflammation, trauma or injury.⁴ The aim of therapy for acute pain is to treat the underlying cause of pain and to

¹ Department of pharmacology, clinical pharmacology and toxicology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia.

² Ob/Gyn Hospital, University Clinical Centar "Dr Dragisa Misovic Dedinje", Belgrade Serbia.

³ Rolf-Detlef Treede, “The International Association for the Study of Pain definition of pain: as valid in 2018 as in 1979, but in need of regularly updated footnotes,” *Pain Rep* 3(2) (2018): e643.

⁴ KP Grichnik, FM Ferrante, “The difference between acute and chronic pain,” *Mt Sinai J Med* 58(3) (1991): 217-20.

interrupt the nociceptive signals. Improperly treated, acute pain increases the body's neuroendocrine and immune responses to stress and can produce early and late adverse systemic effects and complications, with retardation of healing, increased morbidity, mortality, prolonged hospitalization and the transition of acute to chronic pain.⁵

Chronic pain persists over a longer time than acute pain and is usually resistant to most medical treatments.⁶ Chronic pain is defined as persistent or recurrent pain lasting longer than three months.⁷ It often causes severe problems for patients. Chronic pain may be considered a disease state. Chronic pain occurs in about 20% of the adult population, and more often in women and the older population.⁸ Pain often lasts because of inadequate treatment, and many patients suffer for months and years. This condition leads to depression, anxiety, professional disability and deconditioning.⁹ Insomnia is very common in people with chronic pain. It is a consequence of the mechanism of central sensitization, characterized by a state of neuroinflammation and commonly associated with stress or anxiety. Usually, these patients do not respond effectively to the therapy.¹⁰

The treatment of chronic pain is very difficult. There are many discrepancies between the diagnosis and the treatment of chronic pain with regard to ethical issues that must be addressed. The ethical issues associated with chronic pain treatment are numerous. Ethical principles such as autonomy, integrity, beneficence, equity and nonmaleficence should be considered when treatment of chronic pain is considered.

⁵ K. Kirsh, A.K. Vice, S. Passik, "History of Opioids and Opiophobia," in *Pain and chemical dependency*, ed. H. Smith, S. Passik (New York: Oxford University Press, 2008), 3-8.

⁶ Sonja Vucković, Milica Prostran, Milovan Ivanović, Zoran Todorović, Radan Stojanović, Zorica Nesić, Ivana Matić, Slobodan Milovanović, "Opioid analgesics," *Vojnosanit Pregled* 61(4) (2004): 13-21.

⁷ Daniel Z Buchman, Anita Ho, Judy Illes, "You present like a drug addict: patient and clinician perspectives on trust and trustworthiness in chronic pain management," *Pain Med* 17(8) (2016): 1394-1406.

⁸ O. van Hecke, N. Torrance, B.H. Smith, "Chronic pain epidemiology and its clinical relevance," *Br J Anaesth* 111(1) (2013): 13-8.

⁹ Rebecca Dale, Brett Stacey, "Multimodal Treatment of Chronic Pain," *Med Clin North Am* 100(1) (2016): 55-64.

¹⁰ Jo Nijs, Oliver Mairesse, Daniel Neu, Laurence Leysen, Lieven Danneels, Barbara Cagnie, Mira Meeus, Maarten Moens, Kelly Ickmans, Dorien Goubert, "Sleep Disturbances in Chronic Pain: Neurobiology, Assessment, and Treatment in Physical Therapist Practice," *Phys Ther* 98(5) (2018): 325-335.

Also, a patient's dignity should be respected.¹¹ Pain is subjective and should be recognized as such by patients, physicians and nurses. Improving the relationship, communication and trust between patient and doctor is essential for better treatment.

Pain medicine can be demanding, especially in the context of existing economic, official and public environments.¹²

There are many different financial, regional and cultural differences with regard to treating pain. One of them is the lack of identification of pain as a priority in patient care. Another problem is inadequate information about a satisfactory treatment with analgesics.¹³ Additionally, problems in treating chronic pain are as follows: undertreatment of pain, inappropriate and excessive consumption of pharmacologic agents, contradictory information between theory and practice, treatment of chronic pain in vulnerable patients such as the elderly.¹⁴

Pain can exist as an indication of disease and as a phenomenon *per se*.¹⁵ Refractory and chronic pain have complex mechanisms and require diverse specialists, different diagnostic procedures, recordings and treatments. It is an ethical obligation to treat pain. Unfortunately, numerous investigations confirm that pain often goes untreated or undertreated. The American Pain Society presented one study in which 80% of patients after surgical interventions had postoperative pain, with 75% of the patients having moderate, severe or extreme pain.¹⁶ Pain at

¹¹ Karin Fredrikson, Tracy Fasolino, "Pharmacogenetic Testing: The Ethics of Implementing in Clinical Practice for Chronic Pain Patients," *J Pain Palliat Care Pharmacother* 34 (2020): 69-76.

¹² Lilla Náfrádi, Zlatina Kostova, Kent Nakamoto, Peter Schulz, "The doctor-patient relationship and patient resilience in chronic pain: A qualitative approach to patients' perspectives," *Chronic Illn* 14(4) (2018): 256-270.

¹³ Ru-Rong Ji, Andrea Nackley, Yul Huh, Niccolo Terrando, William Maixner, "Neuroinflammation and Central Sensitization in Chronic and Widespread Pain," *Anesthesiology* 129(2) (2018): 343-366.

¹⁴ Ana Sofia Carvalho, Sandra Martins Pereira, Antonio Jácomo, Susana Magalhães, Joana Araújo, Pablo Hernández-Marrero, Carlos Costa Gomes, Michael E. Schatman, "Ethical decision making in pain management: a conceptual framework," *J Pain Res* 11 (2018): 967-76.

¹⁵ James Giordano, Michael E Schatman, "An ethical analysis of crisis in chronic pain care. Part 1. Facts, issues, and problems in pain medicine," *Pain Physician* 11(4) (2008): 483-490.

¹⁶ American Pain Society, "Guidelines on the management of postoperative pain," *J Pain* 17(2) (2016): 131-157.

the end of life in patients with different diagnoses and diseases usually remained untreated. In another study, the authors concluded that almost one in two patients with cancer pain was unrelieved and undertreated.¹⁷ The extent to which the problem of chronic pain is expressed in daily work of healthcare professionals is illustrated by the activities of emergency physicians. In total, 4% of all interventions in an emergency unit consisted of calls from cancer patients. In 2009, in Serbia, in one emergency unit 255 interventions per month and 3060 visits per annum were registered because of pain. Most of these interventions were related to the management of exacerbations of oncological disease, where pain was a predominant symptom.¹⁸ Pharmacotherapy in over 75% of cases ensures the elimination of cancer pain when properly administered.¹⁹

Guidelines for palliative care suggest that adequate pharmacological treatment can eliminate every type of pain in most patients (70-90%). However, everyday practice and research by the World Health Organization show that such treatments, especially in patients suffering from malignant pain, is successful in about 50% of cases. A particular ethical problem is euthanasia in terminal patients.

The treatment of chronic pain is multimodal and requires a multidisciplinary approach that includes different therapeutic modalities. There are guidelines for the treatment and diagnostic techniques for chronic pain. Sound knowledge of pain mechanisms is the basis for an efficient and satisfactory treatment. Physicians with insufficient training cannot help the healthcare system. An interdisciplinary pain management program (PMP) should focus on evidence-based outcomes.²⁰ Pain clinics offer a biopsychosocial approach to treatment with multidisciplinary PMPs. The aim of these programs is to encourage patients to solve their problems with pain and to move on to a gratifying life in spite of the pain.²¹

¹⁷ Robert Swarm, A.M. Abernethy, Judith A. Paice, Doralina L. Anghelescu, et al., "National Comprehensive Cancer Network. Adult Cancer Pain," *J Natl Compr Canc Netw* 11 (8) (2013): 992-1022.

¹⁸ M. Mitrović, B. Jedoksić, S. Petrović, "Opioidi u terapiji hroničnog kancerskog bola," *NC urgent medic* 16(2) (2010): 78-86.

¹⁹ P. Glare, "Choice of opioids and the WHO Ladder," *J Pediatr Hematol Oncol* 33 (2011): 6-11.

²⁰ Robert J. Gatchel, Donald D. McGeary, Cindy McGeary, Ben Lippe, "Interdisciplinary chronic pain management: past, present, and future," *Am Psychol* 69(2) (2014): 119-30.

²¹ Nicholas Hylands-White, Rui V. Duarte, Jon H. Raphael, "An overview of treatment approaches for chronic pain management," *Rheumatol In* 37 (2017): 29-42.

Analgesics such as non-steroidal anti-inflammatory drugs usually only have a modest effect and significant side effects. Opioids are drugs for the treatment of severe pain conditions. Generally, opioids are safe and effective drugs when used properly. The use of opioid analgesics is a particular ethical problem. Worldwide, the phenomenon of opiophobia is recognized as an irrational fear of using and prescribing opioid analgesics opioids by doctors, nurses, patients and relatives.²² Opiophobia is an irrational fear of using and prescribing opioid analgesics.

The physicians' fear of using opioids to treat pain is irrational. Therefore, doctors do not prescribe opioids when indicated by the severity of pain, prescribing them at lower doses than necessary or discontinuing them as soon as the pain is resolved, regardless of the cause of the pain. In this way, patients are denied opioids as the most effective and safe medication for the long-term treatment of some types of chronic pain.²³ Insufficient knowledge of pharmacology and pharmacotherapeutic options of opioid analgesics, aided by opiophobia, often leads to inadequate implementation of pain therapy and the use of insufficiently effective drugs.²⁴ This creates preconditions for poor treatment of patients and inadequate use of all available therapeutic options.

There is also concern about the side effects of opioids. Surveys conducted among physicians show that there is a fear of developing addiction, tolerance and side effects of opioids. Patients often avoid the use of opioids because of fear of tolerance, physical dependence and

²² Ramazan Baldemir, Erkan Yavuz Akçaboy, Özgen Noyan, Zeynep N. Akçaboy, Mustafa Baydar, Şeref Çelik, "An assessment of physicians attitudes toward opioid usage and opiophobia: Results of a survey from a training and research hospital," *Agri* 31 (2019): 23-31.

²³ Andrew Rosenblum, Lisa A. Marsch, Herman Joseph, Russel K. Portenoy, "Opioids and the treatment of chronic pain: controversies, current status, and future directions," *Exp Clin Psychopharmacol* 16 (2008): 405-16. Snežana M. Bošnjak, Martha A. Maurer, Karen M. Ryan, Ivana Popovic, S. Asra Husain, James F. Cleary, Willem Scholten, "A Multifaceted Approach to Improve the Availability and Accessibility of Opioids for the Treatment of Cancer Pain in Serbia: Results From the International Pain Policy Fellowship (2006-2012) and Recommendations for Action," *J Pain Symptom Manage* 52 (2016): 272-83.

²⁴ Snežana Bošnjak, Dušan B. Beleslin, Ljiljana Vučković-Dekić, "Farmakologija kancerskog bola," *Monografije naučnih skupova AMN SLD* 1 (2007): 55-59.

addiction, respiratory depression, etc. In clinical practice, this means that prescribed opioids are frequently not accepted by patients.²⁵

There is also a fear of restrictive regulations that control the prescribing of opioids as narcotics. In practice, an additional problem in the use of these drugs are the legislative and regulative measures for prescribing opioid drugs in different countries.²⁶

Opioids have unofficially allowed a place in the treatment of pain. The stigmas and biases associated with opioids have significantly accentuated the barriers of admission, superiority and teaching with regard to appropriate pain management and community debate of potential strategies to promote needed change. Measures that can improve admission, the quality of pain care and resolve public policy debates about the use of opioids for chronic pain are the first steps to ensure an ethically reasonable approach to chronic pain management in the 21st century.

A big problem of multimodal analgesia for chronic pain patients are interactions between drugs. Usually, chronic pain patients have other comorbidities which need appropriate treatment and the use of different drugs, which increases the risk of possible interactions.²⁷ Interaction can be serious for the patients' health. More importantly, to treat the pain adequately or to treat a serious interaction, represents an ethical issue.

Chronic pain is a significant and costly problem in the United States as well as the rest of the developed world. In the USA, the cost of the treatment of pain is about \$65 billion a year. Pharmacotherapy is very important, but a benefit-cost-effectiveness risk should be included in the decision. Planned interdisciplinary programs for the treatment of chronic pain are good and helpful but expensive.

A special ethical problem is treating pain in the elderly.²⁸ Chronic pain in older adults is connected with special differences, which are age-

²⁵ Michal Graczyk, Alina Borkowska, Molgorzata Krajnik, "Why patients are afraid of opioid analgesics: a study on opioid perception in patients with chronic pain," *Pol Arch Intern Med* 128 (2018): 89-97.

²⁶ Guy Schofield, Idris Baker, Rachel Bullock, Hannah Clare, Paul Clark, Derek Willis, Craig Gannon, Rob George, "Palliative opioid use, palliative sedation and euthanasia: reaffirming the distinction," *J Med Ethics* 46 (2020): 48-50.

²⁷ Emmanuel H. During, John W. Winkelman, "Drug Treatment of Restless Legs Syndrome in Older Adults," *Drugs Aging* 39 (2019): 939-946.

²⁸ Hans Georg Kress, Karsten Ahlbeck, Dominic Aldington, et al, "Managing chronic pain in elderly patients requires a CHANGE of approach," *Curr Med Res Opin* 30 (2014): 1153-64.

related. Pain evaluation is more difficult in old persons. Sometimes, pain can go unreported in the elderly because of dementia and the fear of death.²⁹ Also, other problems in the elderly are specific changes in pharmacokinetics and pharmacodynamics of certain drugs. The use of opioid drugs in the elderly can be difficult due to interactions with other drugs and comorbidities.³⁰ There are insufficient clinical studies about pain in the elderly as a vulnerable category.³¹ It is a special problem to conduct clinical trials with the older population as vulnerable subjects. Informed consent in clinical trials with the elderly can be problematic due to lack of memory and cognitive impairments such as dementia.³² This may be one of the reasons why so few randomized, controlled clinical trials on the use of drugs, especially opioids in the elderly, are available. Also, patients that are enrolled in clinical investigations are not representative of most chronic pain patients.³³

Ethical issues regarding chronic pain are numerous. The barriers to good chronic pain management are complex and multiple: insufficient education, the lack of institutional mechanisms for standardizing the evaluation and treatment of pain, the lack of responsibility for the undertreatment of pain, federal and state permissions for the regulation and adequate use of opioids.³⁴

²⁹ B.R. Ferrell, M.T. Eberts, M. McCaffery, M. Grant, "Clinical decision making and pain," *Cancer Nurs* 14 (1991): 289-297.

³⁰ Milica Prostran, Katarina Savić Vujović, Sonja Vučković, Branislava Medić, Dragana Srebro, Nevena Divac, Radan Stojanović, Aleksandar Vujović, Lepa Jovanović, Ana Jotić, Nataša Cerovac, "Pharmacotherapy of Pain in the Older Population: The Place of Opioids," *Front Aging Neurosci* 8 (2016): 144.

³¹ Sebastiano Mercadante, Antonino Giarratano, "Assessing age and gender in studies of breakthrough pain medications," *Curr Med Res Opin* 30 (2014): 1353-1356.

³² Milica Prostran, Zoran Todorovic, Radan Stojanovic, Tatjana Potpara, Zorica Nesic, elenaJ Lasic, et al, "Bioethics in clinical trials: vulnerable subjects," in *Bioethics and Pharmacology: Ethics in Preclinical and Clinical Drug Development*, ed. Zoran Todorovic, Milica Prostran, Karel Turza (Trivandrum: Research Network, 2012), 87-100.

³³ William Maixner, Roger B. Fillingim, David A. Williams, Shad B. Smith, Gary D. Slade, "Overlapping Chronic Pain Conditions: Implications for Diagnosis and Classification," *J Pain* 17 (2016): 93-107.

³⁴ Volker Tronnier, "Neuromodulation for the Treatment of Chronic Pain - What is Useful?" *Fortschr Neurol Psychiatr* 85 (2017): 223-240.

CONCLUSION

Further clinical studies that examine ethical issues could improve this situation. In an age of rapid medical advances and technological development, it is unacceptable that there is an obstacle to adequate chronic pain medication.

ACKNOWLEDGEMENTS

This work was supported by the Ministry of Education, Science and Technological Development of Serbia (Grant 175023).

REFERENCES

- American Pain Society. "Guidelines on the management of postoperative pain." *J Pain* 17(2) (2016): 131–157.
- Baldemir, Ramazan, AND Erkan Yavuz Akçaboy, Özgen Noyan, Zeynep N Akçaboy, Mustafa Baydar, Şeref Çelik. "An assessment of physicians attitudes toward opioid usage and opiophobia: Results of a survey from a training and research hospital." *Agri* 31 (2019): 23-31.
- Bosnjak, Snežana M., and Martha A. Maurer, Karen M. Ryan, Ivana Popovic, S. Asra Husain, James F. Cleary, Willem Scholten. "A Multifaceted Approach to Improve the Availability and Accessibility of Opioids for the Treatment of Cancer Pain in Serbia: Results from the International Pain Policy Fellowship (2006-2012) and Recommendations for Action." *J Pain Symptom Manage* 52 (2016): 272-283.
- Bošnjak, Snežana, and Dušan B. Beleslin, Ljiljana Vučković-Dekić, "Farmakologija kancerskog bola." *Monografije naučnih skupova AMN SLD*, 1 (2007): 55-59.
- Buchman, Daniel Z., and Anita Ho, Judy Illes. "You present like a drug addict: patient and clinician perspectives on trust and trustworthiness in chronic pain management." *Pain Med* 17(8) (2016): 1394–1406.
- Carvalho, Ana Sofia, and Sandra Martins Pereira, Antonio Jácomo, Susana Magalhães, Joana Araújo, Pablo Hernández-Marrero, Carlos Costa Gomes, Michael E Schatman. "Ethical decision making in pain management: a conceptual framework." *J Pain Res* 11 (2018): 967-976.
- Dale, Rebecca, and Brett Stacey. "Multimodal Treatment of Chronic Pain." *Med Clin North Am* 100(1) (2016): 55-64.

- During, Emmanuel H., and John W Winkelman. "Drug Treatment of Restless Legs Syndrome in Older Adults." *Drugs Aging* 39 (2019): 939-946.
- Ferrell, B.R., and M.T. Eberts, M. McCaffery, M. Grant. "Clinical decision making and pain." *Cancer Nurs* 14 (1991): 289-297.
- Fredrikson, Karin, and Tracy Fasolino. "Pharmacogenetic Testing: The Ethics of Implementing in Clinical Practice for Chronic Pain Patients." *J Pain Palliat Care Pharmacother* 34 (2020): 69-76.
- Gatchel, Robert J., and Donald D. McGeary, Cindy A. McGeary, Ben Lippe. "Interdisciplinary chronic pain management: past, present, and future." *Am Psychol* 69(2) (2014): 119-30.
- Giordano, James, and Michael E. Schatman. "An ethical analysis of crisis in chronic pain care. Part 1. Facts, issues, and problems in pain medicine." *Pain Physician* 11(4) (2008): 483-490.
- Glare, Paul. "Choice of opioids and the WHO Ladder." *J Pediatr Hematol Oncol* 33 (2011): 6-11.
- Graczyk, Michal, and Alina Borkowska, Molgorzata Krajnik. "Why patients are afraid of opioid analgesics: a study on opioid perception in patients with chronic pain." *Pol Arch Intern Med* 128 (2018): 89-97.
- Grichnik, K.P., and F.M. Ferrante. "The difference between acute and chronic pain." *Mt Sinai J Med* 58(3) (1991): 217-20.
- Hecke, O. van, and N. Torrance, B.H. Smith. "Chronic pain epidemiology and its clinical relevance." *Br J Anaesth* 111(1) (2013): 13-18.
- Hylands-White, Nicholas, and Rui V. Duarte, Jon H. Raphael. "An overview of treatment approaches for chronic pain management." *Rheumatol In* 37 (2017): 29-42.
- Ji, Ru-Rong, and Andrea Nackley, Yul Huh, Niccolo Terrando, William Maixner. "Neuroinflammation and Central Sensitization in Chronic and Widespread Pain." *Anesthesiology* 129(2) (2018): 343-366.
- Kirsh, K., and A.K. Vice, S. Passik. "History of Opioids and Opiophobia." In *Pain and chemical dependency*, ed. H. Smith, S. Passik, 3-8. New York: Oxford University Press, 2008.
- Kress, Hans Georg, and Karsten Ahlbeck, Dominic Aldington, et al. "Managing chronic pain in elderly patients requires a CHANGE of approach." *Curr Med Res Opin* 30 (2014): 1153-1164.
- Maixner, William, and Roger B. Fillingim, David A. Williams, Shad B. Smith, Gary D. Slade. "Overlapping Chronic Pain Conditions:

- Implications for Diagnosis and Classification.” *J Pain* 17 (2016): 93-107.
- Mercadante, Sebastiano, and Antonino Giarratano. “Assessing age and gender in studies of breakthrough pain medications.” *Curr Med Res Opin* 30 (2014): 1353–1356.
- Mitrović, M., and B. Jedoksić, S. Petrović. “Opioidi u terapiji hroničnog kancerskog bola.” *NC^X urgent medic* 16(2) (2010): 78-86.
- Náfrádi, Lilla, and Zlatina Kostova, Kent Nakamoto, Peter Schulz. “The doctor-patient relationship and patient resilience in chronic pain: A qualitative approach to patients' perspectives.” *Chronic Illn* 14(4) (2018): 256-270.
- Nijis, Jo, and Oliver Mairesse, Daniel Neu, Laurence Leysen, Lieven Danneels, Barbara Cagnie, Mira Meeus, Maarten Moens, Kelly Ickmans, Dorien Goubert. “Sleep Disturbances in Chronic Pain: Neurobiology, Assessment, and Treatment in Physical Therapist Practice.” *Phys Ther* 98(5) (2018): 325-335.
- Prostran, Milica, and Katarina Savić Vujović, Sonja Vučković, Branislava Medić, Dragana Srebro, Nevena Divac, Radan Stojanović, Aleksandar Vujović, Lepa Jovanović, Ana Jotić, Nataša Cerovac. “Pharmacotherapy of Pain in the Older Population: The Place of Opioids.” *Front Aging Neurosci* 8 (2016): 144.
- Prostran, Milica, and Zoran Todorovic, Radan Stojanovic, Tatjana Potpara, Zorica Nesic, Jelena Lazic. “Bioethics in clinical trials: vulnerable subjects.” In *Bioethics and Pharmacology: Ethics in Preclinical and Clinical Drug Development*, ed. Zoran Todorovic, Milica Prostran, Karel Turza, 87–100. Trivandrum: Research Network, 2012.
- Rosenblum, Andrew, and Lisa A. Marsch, Herman Joseph, Russel K. Portenoy. “Opioids and the treatment of chronic pain: controversies, current status, and future directions.” *Exp Clin Psychopharmacol* 16 (2008): 405-16.
- Schofield, Guy, and Idris Baker, Rachel Bullock, Hannah Clare, Paul Clark, Derek Willis, Craig Gannon, Rob George. “Palliative opioid use, palliative sedation and euthanasia: reaffirming the distinction.” *J Med Ethics* 46 (2020): 48-50.
- Swarm, Robert, and A.M. Abernethy, Judith A. Paice, Doralina L. Anghelescu, et al., “National Comprehensive Cancer Network. Adult Cancer Pain.” *J Natl Compr Canc Netw* 11 (8) (2013): 992-1022.

- Treede, Rolf-Detlef. "The International Association for the Study of Pain definition of pain: as valid in 2018 as in 1979, but in need of regularly updated footnotes." *Pain Rep* 3(2) (2018): e643.
- Tronnier, Volker. "Neuromodulation for the Treatment of Chronic Pain - What is Useful?" *Fortschr Neurol Psychiatr* 85 (2017): 223-240.
- Vucković, Sonja, and Milica Prostran, Milovan Ivanović, Zoran Todorović, Radan Stojanović, Zorica Nesić, Ivana Matić, Slobodan Milovanović. "Opioid analgesics." *Vojnosanit Pregled* 61(4) (2004): 13-21.