

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>



Pharmacotherapy of Rare Diseases in Serbia: Bioethical Challenges and How to Overcome Them

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Abstract

Rare diseases (RDs) represent a wide range of chronic and degenerative disorders that affect less than 1 in 2,000, or 5 in 10,000 people, by definition. Most of those diseases are due to genetic abnormalities (around 80% of cases) and may lead to permanent disability. There are between 6,000 and 8,000 rare diseases and pharmacotherapy is not available for many of them. According to the European Organization for Rare Diseases (EURORDIS), these diseases affect thirty million European Union citizens. It is estimated that there are approximately half a million cases in Serbia.

DOI: 10.22618/TP.AEBIO.20214.231006

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PHARMACOTHERAPY OF RARE DISEASES IN SERBIA: BIOETHICAL CHALLENGES AND HOW TO OVERCOME THEM

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BACKGROUND

A rare disease (RD) is defined as a disease or disorder that affects 1 in 1,500 people, according to the U.S. National Institutes of Health -NIH. In comparison, the European Union defines rare diseases as those affecting less than 1 in 2,000 people or 5 in 10,000 citizens.²

While any rare disease will affect a small number of people, when taken together, all rare diseases (there are over 7,000 today) affect more than 25 million Americans and over 30 million European Union citizens. Although there are no official data, it is estimated that in Serbia half a million people suffer from some of these conditions.³

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² E. Adams, J. Deutsche, E. Okoroh, S. Owens-Mcalister, S. Majumdar, M. Ullman, M-L. Damiano, M. Recht, L. Casto, K. Droze, "An inventory of healthy weight practices in federally funded haemophilia treatment centres in the United States," *Haemophilia: the official journal of the World Federation of Hemophilia* 20(5) (2014): 639-43. K. Ahmad, A. Daliri, J. Mamikhani, "Cost-effectiveness of prophylaxis against on-demand treatment in boys with severe haemophilia in Iran," *Value Health* 12(3) (2009): A133.

³ Rare Diseases Europe (EURORDIS): *About Rare Diseases*, www.eurordis.rs/aboutrare-diseases (accessed: June 15, 2020). Serbian National Organization for Rare Diseases (NORBS): *About Rare Diseases* (Serbian), www.norbs.rs/norbso-retkim-bolestima.php (accessed: June 15, 2020).

We must note that Serbia has made certain progress concerning this topic in the last decade. The National Organization for Rare Diseases in Serbia (NORBS) was formed as a non-governmental, non-profit organization in 2010 with the main focus to improve the quality of life of patients who suffer from RDs in our country. This organization is the main ideological driver of all actions in the country that aim to advance the health, social and bioethical aspects of these patients. Besides this, progress has been made in the laws concerning these disorders. The law on Social protection in 2011 provided four different kinds of support for these persons: financial social assistance, allowance and extended allowance for help and care of another person and one-time financial assistance. Additionally, in 2014, the first legislative framework for patients with rare diseases was made. These amendments suggested the need for the creation of centres for rare diseases, promoted these patients as a special category with a claim to use free health insurance and formed an additional budget in the Ministry of Health in order to invest in orphan drugs.⁴

Still, there are many obstacles and unresolved issues. For example, until today, there is no proper coding system for most RDs in Serbia, accurate and well-timed diagnostics in many cases is still missing, there is no sufficient number of registered orphan drugs, the procedures for their procurement are complicated, etc.

Because of all of the above, education on rare diseases contributes not only to more accurate and timely diagnoses and treatment of particular patients, but also improves the general aspects of this problem such as planning a national strategy, funding, foundation of expert centres etc. Therefore, the role of medical, but also bioethical education is essential in providing a good foundation for present and future doctors involved in this issue.

⁴ *Amendments to the Law on Health Care. Official Gazette Republic of Serbia*, no. 57/2011. (Belgrade: Official Gazzete of the Republic of Serbia, 2011). www.parlament.gov.rs/narodna-skupstina-.871.html (accessed: June 3, 2020). M. Joldic, J. Todorovic, Z. Terzic-Supic, "The needs of patients with rare disease in Serbia: Why do we need National Strategy for rare disease?" *Health & Social Care in the Community* (2019): 1-10. Branislava Medić Brkić, Bojan Stopić, Katarina Savić Vujović, Nevena Divac, Sonja Vučković, Radan Stojanović, Dragana Srebro, Miloš Basailović, Milica Prostran, "Pharmacotherapy of Rare Diseases in Serbia: The Current State of Art," in "*Rare Diseases*," ed. Zhan He Wu (IntechOpen), DOI: 10.5772/intechopen.91262. www.intechopen.com/books.

BARRIERS IN THE PHARMACOTHERAPY OF RARE DISEASES

Patients affected by rare diseases, in general, face many problems. They are often misdiagnosed or the diagnosis is delayed due to several problems: lack of awareness among physicians, lack of expertise, unavailability and/or high costs of diagnostic tests and drugs for rare diseases (orphan drugs). According to the National Organization of Patients with Rare Diseases in Serbia (NORBS), many diagnostic procedures have to be conducted abroad and the process comprises many difficulties: high costs, travel expenses or transportation of biological material etc. Although national legislation ensures the availability of drugs for those diseases, pharmacotherapy is faced with a lot of problems. Licensed drugs are not always or not readily available and provision of unlicensed medicines is very difficult due to legislative obstacles.⁵

The reason for this situation is the fact that pharmaceutical companies are not motivated to invest in the development and distribution of low-consumption drugs on the market. They need to invest a significant financial resource in orphan drugs but often struggle to recover costs through sales. Besides this, there are other obstacles regarding drugs for rare diseases. There are no Orphan Drug Regulations and cross-sector sponsorship.⁶

Additionally, clinical trials that examine drugs for rare diseases also face many difficulties and limitations. Performing clinical studies properly, in this case, is difficult because the number of potential participants is low, there are numerous challenges regarding uniform diagnostic criteria, lack of reliable patient registries, use of placebo group

⁵ B. Medić, N. Divac, B. Stopić, K. Savić Vujović, A. Glišić, N. Cerovac, M. Prostran, "The attitudes of medical students towards rare diseases: A cross-sectional study," *Vojnosanitetski Pregled* 73 (2015): 94.

⁶ M. E. Haffner, "Adopting orphan drugs – two dozen years of treating rare diseases," *N Engl J Med* 354 (5) (2006): 445–7. R. Fiorentino, G. Liu, A. R. Pariser, A. E. Mulberg, "Cross-sector sponsorship of research in eosinophilic esophagitis: a collaborative model for rational drug development in rare diseases," *J Allergy Clin Immunol* 130 (3) (2012): 613–6. M. Dunoyer, "Accelerating access to treatments for rare diseases," *Nat Rev Drug Discov* 10 (7) (2011): 475–6.

(which may not be ethical because of the severity of some rare diseases), technical problems to design this kind of clinical trials etc.⁷

In addition to clinicians, researchers are also not particularly interested in dealing with and performing research on rare diseases and orphan drugs. There is a logical explanation for this. It is difficult to obtain relevant and reliable data on rare diseases because of data heterogeneity, outcomes and measurement techniques may differ from one country to another, even for the same diseases. The second problem represents the dissemination of the results of some RD examinations. Journal editors may hesitate to publish studies with a narrow audience and small impact.⁸

BIOETHICAL CHALLENGES REGARDING PHARMACOTHERAPY OF RARE DISEASES

There is a lot of bioethical controversy and open questions regarding rare diseases and their pharmacotherapy. Research on rare diseases should satisfy the ethical conditions that apply to human subjects generally.

Patients suffering from RDs could be recognized as vulnerable subjects. It is well known that most of these diseases represent chronic, degenerative, and life-threatening conditions with an unknown or genetic origin. Besides this, more than half of all patients are children.⁹

Some RDs could have an overwhelming influence on all aspects of the patients' lives and their careers. Also, the development and availability of orphan drugs could threaten basic bioethical principles.

⁷ R. J. Lilford, J. G. Thornton, D. Brauholtz, "Clinical trials and rare diseases: a way out of a conundrum," *BMJ (Clinical research ed)*. 311(7020) (1995): 1621–5. M. Luisetti, I. Campo, R. Scabini, M. Zorzetto, Z. Kadija, F. Mariani, I. Ferrarotti, "The problems of clinical trials and registries in rare diseases," *Respir Med* 104 (Suppl 1) (2010): S42–4. S. Groft, P. de la Paz, "Rare diseases – avoiding misperceptions and establishing realities: the need for reliable epidemiological data," *Adv Exp Med Biol* 686 (2010): 3–14.

⁸ M. Pai, C. H. T. Yeun, E. A. Akl, "Strategies for eliciting and synthesizing evidence for guidelines in rare diseases," *BMC Med Res Methodol* 19(1) (2019): 67.

⁹ Z. Todorović, M. Prostran, B. Medić, M. Vučinić, "Bioethics and pharmacology," in *Bioethics and Pharmacology: Ethics in Preclinical and Clinical Drug Development*, eds. Z. Todorović, M. Prostran, K. Turza, K. Kerala (Transworld Research Network, 2012), 7–13. M. Prostran, Z. Todorović, R. Stojanović, T. Potpara, Z. Nešić, J. Lazić, B. Medić, "Bioethics in clinical trials: Vulnerable subjects," in *Bioethics and Pharmacology: Ethics in Preclinical and Clinical Drug Development*, eds. Z. Todorović, M. Prostran, K. Turza, K. Kerala (Transworld Research Network, 2012), 87–100.

However, participation in clinical trials and research on rare diseases can affect each of the four basic bioethical principles. We have previously discussed four commonly accepted principles of medical ethics regarding the issue of rare diseases, excerpted from Beauchamp and Childress. They include the: (1) principle of respect for autonomy, (2) principle of non-maleficence, (3) principle of beneficence, and (4) principle of justice.¹⁰ At this point, we will point out some of the most important and challenging facts regarding this topic.

- Autonomy and informed consent

The lack of alternatives can significantly affect patients' free will to participate in rare disease research. This is especially important when patients need to sign an informed consent in order to participate in a clinical trial for orphan drugs.

In addition, we must emphasize here that a large percentage of these diseases are of genetic origin and that the largest number of patients are children, who cannot make decisions independently.

- Beneficence and maleficence

Clinical studies and research on rare diseases can challenge this bioethical principle in several ways. We have already discussed the dangers of including a placebo control group of patients in this type of study. However, there are other limitations such as specific interventions and methods of administering these substances, insufficiently reliable data on such therapies, insufficiently trained experts and adequate medical equipment. Clinical trials for rare and ultra-rare diseases typically involve a limited number of research sites recruiting from a small pool of patients dispersed over a large geographical area. In this situation, individuals and their families are required to travel great distances, often at high cost personally and financially.¹¹

- Justice

The bioethical principle in this kind of research is often considered in relation to participant selection and ensuring that the risks and benefits

¹⁰ T. Beauchamp, J. Childress, *Principles of Biomedical Ethics*, 7th ed. (New York: Oxford University Press, 2013): 10-17.

¹¹ L. Gelinás, B. Crawford, A. Kelman, B. E. Bierer, "Relocation of study participants for rare and ultra-rare disease trials: Ethics and operations," *Contemp Clin Trials* 84 (2019): 105812

of research participation are distributed equitably among individuals and social groups.¹²

However, in many cases, this is not possible because there are no standards and guidelines for many RDs or their differences from one county to another. In these situations, an offer of relocation and participation in some trials may be the best option available, but the question is whether this opportunity will be equally accessible to all. The answer is probably no.

THE IMPACT OF BIOMEDICAL EDUCATION ON ATTITUDES REGARDING RARE DISEASES

We considered it crucial to examine different aspects of knowledge and attitudes regarding rare disease issues in Serbia. In order to do this, we performed several surveys among medical students, medical doctors and pharmacists, as well as among a group of patients suffering from rare neurological diseases.¹³

Generally, our respondents were highly interested in expressing their attitudes regarding the issue of rare diseases and their treatment in our country and we had a high percentage of provided answers.

A survey conducted among third- and sixth-year medical students showed that final-year students did not make significant progress regarding knowledge and attitudes on rare diseases and their pharmacotherapy in comparison to their younger fellows. Nevertheless, their answers indicated that they understand the problem and the importance of dealing with this issue in our country.

In the second part of our examination, our respondents from the physicians and pharmacists voluntarily participated in our survey. Although these were health professionals who meet patients with rare

¹² National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research The Belmont Report. <https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html> (accessed: June 1, 2020).

¹³ B. Medic, B. Stopic, S. Peric, V. Rakocevic Stojanovic, D. Lavrnjic, K. Savic Vujovic, S. Vuckovic, N. Divac, R. Stojanovic, D. Srebro, M. Prostran, "How to Live with Rare Diseases in Serbia: The Knowledge and Attitudes of Patients Regarding Medical, Societal and Bioethical Aspects of this Issue," *International Journal of Humanities Social Sciences and Education* 3(2) (2016): 24-30. B. Medić, Z. Todorović, K. Savić Vujović, R. Stojanović, M. Prostran, "Oboleli od retkih bolesti kao vulnerabilni ispitanici u kliničkim studijama," *JAHIR* 8(4)(2013): 715-724.

diseases, most of them believed they are not sufficiently educated on this issue. However, they recognized the key problems of such patients in our community: lack of scientific knowledge, complicated procedures for the procurement of drugs, the lack of a sufficient number of registered medicines for these diseases etc.

Finally, in the third part of our work, we performed a cross-sectional study among outpatients and inpatients (Neurology Clinic, Department for Neuromuscular Disorders, Clinical Center of Serbia) who suffered from rare neurological diseases. Results showed that only half of the participants knew that they suffered from a rare disease and in general they have shown very poor knowledge on this subject in our country. Besides this, only 16.6% of examined patients were part of some rare diseases patients' organizations and just a quarter of our respondents (26.6%) agreed to participate in clinical trials concerning orphan drugs. The improvement of the pharmacotherapy of rare diseases in Serbia, medical professionals and patients can be achieved by enhancement of general and scientific knowledge, well-timed and appropriate diagnostics, simplified procedures for drug procurement, registration of more orphan drugs, etc.

CONCLUSION

Our research has shown that it is necessary to improve knowledge and attitudes among all participants of the health system in the country (present and future medical doctors and pharmacists, patients and their families, regulatory bodies and general population).

We firmly believe that this is the right time to start a comprehensive and constructive debate in society on this topic, both from a medical and legal perspective. Each of these participants should make a contribution in order to improve the position of this group of patients.

The first step is education that should relate not only to medical and legal issues, but also to the ethical issues of patients with rare diseases. As professors at the Medical Faculty of the largest university in Serbia, we believe that the beginning of this education should have started among students of medicine and pharmacy, but also among students of law and philosophy. This is the critical point for conducting a public discussion in order to significantly improve the position of rare diseases patients' in our community in future.

ACKNOWLEDGEMENTS

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

REFERENCES

- Adams, E., and Deutsche J., Okoroh E., Owens-Mcalister S., Majumdar S., Ullman M., Damiano M.L., Recht M., Casto L., Droze K. "An inventory of healthy weight practices in federally funded haemophilia treatment centres in the United States." *Haemophilia: the official journal of the World Federation of Hemophilia* 20(5) (2014): 639-43.
- Ahmad K., and Daliri A., Mamikhani J. "Cost-effectiveness of prophylaxis against on-demand treatment in boys with severe haemophilia in Iran." *Value Health* 12(3) (2009): A133.
- Amendments to the Law on Health Care. Official Gazette Republic of Serbia* 2011, no. 57/2011. Belgrade: Official Gazzete of the Republic of Serbia. www.parlament.gov.rs/narodna-skupstina-.871.html. Accessed: June 3, 2020.
- Beauchamp T., and Childress J. *Principles of Biomedical Ethics*, 7th ed. New York: Oxford University Press, 2013.
- Dunoyer, M. "Accelerating access to treatments for rare diseases." *Nat Rev Drug Discov* 10 (7) (2011): 475-6.
- Fiorentino, R., and Liu G., Pariser A.R., Mulberg A.E. "Cross-sector sponsorship of research in eosinophilic esophagitis: a collaborative model for rational drug development in rare diseases." *J Allergy Clin Immunol* 130 (3) (2012): 613-6.
- Gelinas L., and Crawford B., Kelman A., Bierer B.E. "Relocation of study participants for rare and ultra-rare disease trials: Ethics and operations." *Contemp Clin Trials* 84 (2019): 105812. doi: 10.1016/j.cct.2019.105812.
- Groft, S., and de la Paz P. "Rare diseases - avoiding misperceptions and establishing realities: the need for reliable epidemiological data." *Adv Exp Med Biol* 686 (2010): 3-14.
- Haffner, M.E. "Adopting orphan drugs--two dozen years of treating rare diseases." *N Engl J Med* 354 (5) (2006): 445-7.
- Joldic, M., and Todorovic J., Terzic-Supic Z. "The needs of patients with rare disease in Serbia: Why do we need National Strategy for rare disease?" *Health & Social Care in the Community* (2019): 1-10.

- Lilford, R.J., and Thornton J.G., Brauholtz D. "Clinical trials and rare diseases: a way out of a conundrum." *BMJ (Clinical research ed)*. 311(7020) (1995): 1621-5.
- Luisetti, M., and Campo I., Scabini R., Zorzetto M., Kadrija Z., Mariani F., Ferrarotti I. "The problems of clinical trials and registries in rare diseases." *Respir Med* 104 (Suppl 1) (2010): S42-4.
- Medić Brkić, B., and Stopić B., Savić Vujović K., Divac N., Vučković S., Stojanović R., Srebro D., Basailović M., Prostran M. "Pharmacotherapy of Rare Diseases in Serbia: The Current State of Art", in *Rare Diseases*, ed. Zhan He Wu. IntechOpen. DOI: 10.5772/intechopen.91262. <https://www.intechopen.com/books>.
- Medić, B., and Divac N., Stopić B., Savić Vujović K., Glišić A., Cerovac N., Prostran M. "The attitudes of medical students towards rare diseases: A cross-sectional study." *Vojnosanitetski Pregled* 73 (2015).
- Medić B., and Stopić B., Perić S., Rakočević Stojanović V., Lavrić D., Savić Vujović K., Vučković S., Divac N., Stojanović R., Srebro D., Prostran M. "How to Live with Rare Diseases in Serbia: The Knowledge and Attitudes of Patients Regarding Medical, Societal and Bioethical Aspects of this Issue." *International Journal of Humanities Social Sciences and Education* 3(2) (2016): 24-30.
- Medić B., and Todorović Z., Savić Vujović K., Stojanović R., Prostran M. "Oboleli od retkih bolesti kao vulnerabilni ispitanici u kliničkim studijama." *JAFHR* 8(4) (2013): 715-724.
- National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research The Belmont Report. <https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html>. Accessed: June 1, 2020.
- Pai, M., and Yeung C.H.T., Akl E.A. "Strategies for eliciting and synthesizing evidence for guidelines in rare diseases." *BMC Med Res Methodol* 19(1) (2019).
- Prostran M., and Todorović Z., Stojanović R., Potpara T., Nešić Z., Lazić J., Medić B. "Bioethics in clinical trials: Vulnerable subjects." In *Bioethics and Pharmacology: Ethics in Preclinical and Clinical Drug Development*, ed. Todorović Z., Prostran M., Turza K., 87-100. Transworld Research Network, 2012.
- Rare Diseases Europe (EURORDIS): *About Rare Diseases*. www.eurordis.rs/aboutrare-diseases. Accessed: June 15, 2020.

Serbian National Organization for Rare Diseases (NORBS). *About Rare Diseases* (Serbian). www.norbs.rs/norbso-retkim-bolestima.php. Accessed: June 15, 2020.

Todorović, Z., and Prostran M., Medić B., Vučinić M. “Bioethics and pharmacology.” In *Bioethics and Pharmacology: Ethics in Preclinical and Clinical Drug Development*, ed. Todorović Z., Prostran M., Turza K., 7-13. Transworld Research Network, 2012.