

Health Equity Consideration in Cochrane Systematic Reviews and Primary Studies on Add-on Therapy for Refractory Focal Epilepsy Treatment

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Abstract

Objective: Health equity is defined as the absence of unequal and avoidable factors in health differences among populations. Several add-on treatments have been suggested for refractory epilepsy and epilepsy unresponsive to usual treatments in systematic reviews. The current study assessed equity concerns in Cochrane systematic reviews and original studies on additive therapies used for refractory focal epilepsy because identifying the reasons for injustice is the first step in eradicating health inequality.

Methods: Cochrane systematic reviews and their primary studies on add-on therapy for treatment-resistant focal epilepsy in adults published in the Cochrane library in the last 10 years (until the end of 2022) were gathered. Two researchers independently reviewed the PROGRESS criteria in the studies based on the guide for each of the primary and review studies.

Results: In the present study, 7 systematic reviews and 54 primary studies were included. based on the findings of our study, all review studies and 81.5% of the original studies were conducted in high-income countries. none of the articles mentioned the issue of justice in health or PROGRESS criteria. However, all of the articles mentioned gender distribution and patients' place of residence, and about 35% of the original articles also mentioned patients' race. None of these factors were analyzed as a criterion for group comparison or as a criterion for influencing the treatment process.

Conclusion: The Cochrane-related reviews confirm that PROGRESS criteria are rarely considered in trials of interventions linked to add-on therapies for treatment-resistant focal epilepsy.

Keywords: Health equity, refractory focal epilepsy, systematic reviews

INTRODUCTION

Epilepsy is one of the most common and serious neurological diseases that affects approximately 70 million people worldwide. Epilepsy occurrence has a two-fold pattern, and the highest risk of occurrence is in infants and the elderly; Emergence of epilepsy depends on a combination of environmental risk factors and underlying genetic predisposition.¹ Despite the existence of more than 20 types of anti-epileptic drugs, seizures are still not well controlled in approximately 30% of patients.² Drug-resistant epilepsy does not respond to two or more antiepileptic drugs prescribed as monotherapy or polytherapy for a sufficient time.³ Before further consideration, conditions that mimic drug resistance, such as misdiagnosis, insufficient dosage, inappropriate medication, and low patient compliance, must be ruled out and then referred to specialized epilepsy centers.³ Because drug-resistant epilepsy can be dangerous and greatly affect patients' quality of life, early diagnosis, referral, and treatment are essential.⁴ So far, many research and clinical trials have been conducted on add-on therapies for drug-resistant focal epilepsies, and various drugs such as felbamate, lamotrigine, zonisamide, clonazepam, rufinamide, etc., and the effects of each on epilepsy have been investigated.⁵⁻⁸

Health equity is the absence of unfair and avoidable factors in health between and within populations, and it is a priority for health-related research.⁹ Health justice includes access to health care and equal opportunities to achieve health.¹⁰ Differences in receiving medical and health services between groups may be due to inequality in factors such as social and economic characteristics. Health disparities in

almost all health problems persist and are worsening, both within and between countries. For example, people living in the poorest countries have at least 30 years less life expectancy than people living in the richest countries. In low- and middle-income countries, the under-five mortality rate is 64.6 deaths per 1,000 births among the poor and 31.3 per 1,000 births among the wealthy.¹¹ According to the Global Child Mortality Update, the disparity in under-five mortality between high- and low-income regions is widening as sub-Saharan Africa is estimated to bear 60% of the global burden of under-five mortality by 2050.^{12,13}

The World Health Organization established the Commission on Social Determinants of Health in 2006 and published its final report in 2008 to assess the evidence for reducing health inequalities.¹⁴ Health inequality is defined as the “poor health of the poor” within and between countries due to the “unequal distribution of power, income, goods and services, globally and nationally, resulting in immediate and visible injustice in their access to health care and education, working and leisure conditions, homes, communities, towns or cities-and their chances of living a flourishing life”.¹⁴ Such health inequalities are not only for moral and ethical reasons but also for economic reasons, and should be considered.¹⁵ Increasing evidence of the effectiveness of interventions to reduce health inequalities, both within and between countries, as well as methods for assessing health equity in systematic reviews, such as the Cochrane Handbook chapter about justice and specific populations.¹⁶

Health justice and related studies are becoming a big and fundamental pillar of research. According to the review of such articles on other topics, it has been seen that this principle has not been valued as much as it should be. Regarding the treatment of drug-resistant focal epilepsies, according to the clinical trials of various types of drugs, there is no mention of observing the principles of justice and equality in these cases. According to the abovementioned cases, attention to health justice has a special place among this category of patients. By studying this field and knowing these factors, we can obtain results that can be adapted to most people or societies and have a higher value by eliminating or controlling these inequalities in studies and experiments and helpful in health-related policies.

MAIN POINTS

- Health equity involves the absence of unfair and avoidable differences in health within and between populations. Health justice encompasses access to healthcare and equal opportunities to achieve health.
- Disparities in healthcare access and outcomes persist globally, with significant differences observed between countries and within populations. Social and economic factors influence these disparities.
- Despite the growing importance of health equity, studies, including clinical trials on drug-resistant epilepsy treatments, often overlook the principles of justice and equality. This highlights the need for greater attention to health justice in research and healthcare policies.
- Addressing health inequalities in research and clinical practice can generate results and policies that benefit most people and societies, ultimately leading to more equitable healthcare outcomes.

METHODS

The Cochrane systematic review articles on treatments related to add-on therapies for refractory focal epilepsy in adults from 2011 to 2021 were included in the study. Studies on other diseases in the age range other than adults were excluded from the study.

We also extracted and considered the studies included in each of these review articles as primary studies; based on the location of the study and World Bank classification, we divided the country conducting the study into two groups: high income and low income. Information related to the type of study, sample size, results, location, and budget was also extracted from each study. Two researchers independently reviewed the PROGRESS criteria (Table 1) separately based on the guide (O’Neil reference) for each of the primary and review studies.¹⁷ The contradiction between the extracted data among the researchers was resolved by a third member.

The study protocol was approved by the Ethics Committee of the Iran University of Medical Sciences under the ethical approval code IR.IUMS.FMD.REC.1400.200, date: 20.06.2021.

Table 1. PROGRESS criteria

Place of residence	It is classified as rural, urban, and poor urban areas; It also includes high, middle, and low-income countries.
Race/ethnicity/culture	Refers to the patient’s ethnic, racial, and cultural background as well as language. Race is defined from a biological point of view, while ethnicity and culture include social aspects. Biological differences are not considered unfair unless their manifestation is avoidable.
Occupation	It includes various conditions such as unemployment, part-time jobs, informal workers, and unsafe work environments.
Gender	It includes all social, economic, and cultural characteristics and opportunities and it is a type of role which are determined for both sexes, male and female (based on the phenotype and appearance of the person). This measure includes socially constructed rules and other characteristics that society associates with gender.
Religion	The belief path of people is called religion. This criterion considers the injustices that limit access to health services for a specific subgroup of the population with a specific religious orientation or without any religious orientation.
Education	It refers to the degree of education obtained from reputable educational institutions such as schools and universities. It is important because it affects the type of employment and consequently the income of the person. Also, educated people have more knowledge about health and preventive measures.
Socio-economic level	Objectively measured based on a person’s job, education, and income. This factor determines the adequacy of many components affecting health, such as living conditions and access to fresh and healthy food.
Social capital	It includes the level of trust between community members, civil participation, and the desire of members of a community to help each other and strengthen their political relationships. In general, it includes the amount of support from people around and at the community level.

In general, PROGRESS includes: P: Place of residence, R: Race/ethnicity/culture, O: Occupation, G: Gender, R: Religion, E: Education, S: Socio-economic level, S: Social capital

Statistical Analysis

We used Statistical Package for the Social Sciences version 22 software for statistical analysis of the data. The results for quantitative variables are expressed as mean±standard deviation and for qualitative variables as percentages.

RESULTS

A total of 7 systematic reviews of add-on therapy for refractory focal epilepsy and 54 primary studies were examined. Information on each systematic review included is presented in Table 2.

The results obtained are that all the articles mentioned the two criteria of patients' gender and place of residence; in 19 studies (35.18%), in addition to gender and place of residence, race was also mentioned, but other PROGRESS criteria were not mentioned in any study (Table 3).

DISCUSSION

There is growing evidence that systematic reviews of the best available evidence are the main source of information for determining evidence-based policy and practice and that systematic reviews are a useful basis for decision-making because they

Table 2. Information on included systematic reviews

Title	Number of included studies	Sample size	Country of origin
Felbamate add-on therapy for drug-resistant focal epilepsy ¹⁸	4	236	HIC
Topiramate add-on therapy for drug-resistant focal epilepsy ¹⁹	11	1650	HIC
Vigabatrin add-on therapy for drug-resistant focal epilepsy ²⁰	11	756	HIC
Pregabalin add-on for drug-resistant focal epilepsy ²¹	11	3949	HIC
Carisbamate add-on therapy for drug-resistant focal epilepsy ²²	4	2211	HIC, LIC
Zonisamide add-on therapy for focal epilepsy ⁸	7	1636	HIC
Tiagabine add-on therapy for drug-resistant focal epilepsy ²³	6	948	HIC

HIC: High-income countries, LIC: Low-income countries

Table 3. The PROGRESS dimensions considered in systematic reviews and primary studies

Progress	Reviews	Primary studies
Place of residence	7 (100%)	54 (100%)
Race/ethnicity/culture	0	18 (33.3%)
Occupation	0	0
Gender	7 (100%)	54 (100)
Religion	0	0
Education	0	0
Socioeconomic status	0	0
Social capital and networks	0	0

reduce the likelihood of bias and are a reliable source for clinical practice.^{24,25}

In this study, we examined a total of seven systematic reviews and 54 articles used in the review studies. All review studies were conducted in high-income countries, and 81.5% of the original studies were also conducted in high-income countries, and only 18.5% of them were multi-centric and included low-income countries. None of the studies were conducted only in low-income countries. Based on the findings of our study, none of the articles mentioned the concept of health equity or PROGRESS criteria. However, all the articles mentioned the factors of gender and place of residence of the patients in their findings, and approximately 35% of the original articles also mentioned the race of the patients in addition to the place of residence and gender.

Our findings were consistent with previous studies in the field. As in the study of Tugwell et al.²⁶ about rheumatoid arthritis and its related interventions, among early studies, gender was the most mentioned variable, followed by education level and race/ethnicity. PROGRESS dimensions were mentioned in less than 50% of systematic reviews. Disadvantaged communities were mentioned in only 5% of the primary studies. In general, in early studies on interventions in the field of rheumatoid arthritis, few variables of health inequality criteria were mentioned. In the study by Evans et al.²⁷ on equity related to systematic reviews and primary studies on cataracts, among 85 studies, only one considered the PROGRESS criteria as an inclusion. Overall, the PROGRESS factors that indicate equality were not mentioned in these studies. The same results were found in Cochrane systematic reviews related to HIV infection.²⁸ In another study, it was found that in the studies that conducted strategies to improve the quality of life of diabetic patients, less than one-third of the trials were concerned with the inclusion of health equity criteria.²⁹

The PROGRESS framework was first proposed by Evans et al. in 2003.²⁷ Although there are several other frameworks available for assessing equality, we chose this framework because it is recommended by the Campbell and Cochrane Equity Methods Group and included in the reporting guidelines for systematic reviews in 2012 and intervention studies in 2017.^{30,31} However, not all components of the PROGRESS framework are relevant to all systematic reviews or primary studies. For example, if all participants are from the same place and have similar ethnicities or languages/religions, inequality on these dimensions may not be a concern. However, sometimes people are excluded from studies for reasons such as language or inability to participate; therefore, a higher awareness of equality issues on the part of trial conductors is important.³²

One of the benefits of conducting such studies is to assess the extent to which researchers consider factors related to health equity; however, we were unable to analyze the impact of equity-related factors on study outcomes. The effectiveness of interventions often varies depending on the participating population and the existing health system. Based on the limited primary data we have from targeted and public trials, it is difficult to draw firm conclusions about which health equity interventions or strategies are effective or ineffective in reducing health disparities and/or improving health outcomes for disadvantaged groups.

Study Limitations

The study's limitations include a restricted focus on Cochrane systematic reviews and their primary studies within the past decade, potentially excluding relevant research from other databases or earlier periods. Moreover, the predominant inclusion of studies conducted in high-income countries limits the generalizability of findings to diverse global populations. Despite assessing studies for health equity using PROGRESS criteria, the absence of explicit consideration for health justice and limited analysis of factors such as race or socioeconomic status may overlook important determinants of health disparities.

CONCLUSION

In conclusion, the findings of this study on Cochrane systematic reviews and their primary studies indicate a significant lack of health equity and thus considerable improvement in the proportion of studies that examine equality and the range of equality factors that can be reported and analyzed. Therefore, health equity dimensions can be routinely considered during clinical intervention and randomized controlled trial studies in addition to the usual items of age, gender, comorbidities, and place of residence.

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Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of the Iran University of Medical Sciences under the ethical approval code IR.IUMS.FMD.REC.1400.200, date: 20.06.2021.

Informed Consent: Consent form was filled out by all participants.

Authorship Contributions

Surgical and Medical Practices: Z.M., Concept: Z.M., B.S., Design: Z.M., B.S., Data Collection or Processing: S.S., P.M., R.M., Analysis or Interpretation: S.S., B.S., Literature Search: S.S., P.M., R.M., Writing: S.S., Z.M., P.M., R.M.

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