

Ethical issues related to the access to orphan drugs in Brazil: the case of mucopolysaccharidosis type I

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ABSTRACT

Background/Aims Mucopolysaccharidosis type I (MPS I) is a rare lysosomal storage disorder treated with bone marrow transplantation or enzyme replacement therapy with laronidase, a high-cost orphan drug. Laronidase was approved by the US Food and Drug Administration and the European Medicines Agency in 2003 and by the Brazilian National Health Surveillance Agency in 2005. Many Brazilian MPS I patients have been receiving laronidase despite the absence of a governmental policy regulating access to the drug. Epidemiological and treatment data concerning MPS I are scarce. This study aims to present a demographic profile of Brazilian patients with MPS I, describe the routes of access to laronidase in Brazil, and discuss associated ethical issues relating to public funding of orphan drugs.

Methods In this cross-sectional observational study, data were collected nationwide between January and September 2008 from physicians, public institutions and non-governmental organisations involved with diagnosis and treatment of MPS I, using two data collection instruments specifically designed for this purpose.

Results The minimum prevalence of MPS I in Brazil was estimated at 1/2 700 000. Most patients (69.8%) were younger than 15 years; 60 (88.2%) received laronidase. The most common route of access to the drug was through lawsuits (86.6%).

Conclusions In Brazil, MPS I is predominantly a paediatric illness. Even though the cost of laronidase treatment is not officially covered by the Brazilian government, most MPS I patients receive the drug, usually through litigation. This gives rise to major ethical conflicts concerning drug access in a low-resource context. The Brazilian health policy framework lacks evidence-based clinical protocols for the distribution of orphan drugs.

Mucopolysaccharidosis I (MPS I) is a rare, multi-system lysosomal storage disease caused by deficiency of the enzyme α -L-iduronidase. The main organ systems affected are the bones, joints, upper and lower airways, heart, cornea and central nervous system, and the severity of clinical manifestations is highly variable.¹ MPS I is classically associated with three distinct phenotypes: a severe form (Hurler syndrome), a moderately severe subtype (Hurler–Scheie syndrome) and an attenuated or mild form (Scheie syndrome). Patients with the severe subtype are usually diagnosed with MPS I before the age of 2 years, and experience rapid progression of symptoms, with substantial limitations in quality of life and mental retardation. Death usually occurs before the age of 10 years. In

the moderate form, systemic involvement usually becomes evident at a later age, between 3 and 8 years, and intelligence is normal in most patients. Survival into adulthood is not unusual. In the mildest form of MPS I, symptoms are predominantly bone-related and usually appear between the ages of 5 and 15 years. Life expectancy may be close to normal, and may be shortened by cardiac involvement. MPS I is a classic example of orphan disease (it is a chronic, degenerative, debilitating, inherited condition associated with low life expectancy), even though the prevalence of MPS I is known only at birth—approximately 1/100 000 newborns (according to European criteria, designation as an orphan disease requires a maximum prevalence of 5/10 000).^{2 3}

There is no cure for MPS I. Current treatment options fall into one of two categories: supportive/palliative or specific (enzyme replacement therapy (ERT) and bone marrow transplantation (BMT)). ERT consists of periodic intravenous administration of laronidase, the recombinant form of α -L-iduronidase. Key limitations of ERT include the need for repeated administration and the inability of laronidase to reach certain target organs, such as the central nervous system and bone. BMT, in turn, carries high morbidity and mortality rates (far higher than those of ERT) but has beneficial effects on the central nervous system if carried out at an early age. Currently, BMT is indicated in the most severe cases of MPS I, as long as patients are no older than 24 months.⁴ There are no published prospective clinical trials of BMT for MPS I, and no studies have yet compared the efficacy or effectiveness of BMT versus ERT in this condition.

Laronidase is a typical orphan drug: it is a high-cost medicinal product (the average yearly treatment cost for a patient weighing 20 kg is in the region of US\$350 000) used in the treatment of a rare disease.⁵ In April 2003, laronidase was approved in the USA by the US Food and Drug Administration (FDA) for the treatment of patients with the severe (Hurler) and moderate (Hurler–Scheie) forms of MPS I and of patients with the mild form (Scheie) who have moderate to severe symptoms.⁶ In June of the same year, the drug was approved by the European Medicines Agency (EMA) to treat non-neurological symptoms of MPS I.⁷ Approval was based on the findings of Wraith *et al*,⁸ the only double-blind, placebo-controlled, phase III trial of laronidase published thus far. The study included 45 patients with MPS I randomly assigned to receive weekly

laronidase or placebo for 26 weeks. Patients in the treatment group showed significant improvement in forced vital capacity and the apnoea–hypopnoea index and a significant reduction in hepatomegaly and urinary glycosaminoglycan excretion, but no significant differences in the 6-min walk test, joint mobility, or quality of life. No severe adverse events were reported in the treatment arm.

There is a dearth of epidemiological studies of MPS I in the Brazilian population. Data from the MPS Brazil Network (*Rede MPS Brasil*) show 87 Brazilian patients with MPS I registered between April 2004 and October 2007, but provide no information on patient survival.⁹ Laronidase was granted marketing authorisation by the Brazilian National Health Surveillance Agency (ANVISA) in August 2005, but it is not covered as part of the Brazilian Health Department's specialised pharmaceutical assistance programme, and no clinical protocol and therapeutic guideline (PCDT in the Portuguese acronym) for its use has been issued.¹⁰ BMT is also a high-cost procedure and, when used as a treatment for MPS I, is not covered by any government programmes; nevertheless, as most MPS I patients in Brazil receive a late diagnosis, the treatment of choice is almost invariably ERT.

Even though official public coverage of laronidase is unavailable in Brazil, a country with a universal-access public health-care system, an unknown number of MPS I patients are being treated with the drug through undetermined routes of access. Before this study, the authors suspected that, in several cases, access to the drug was probably secured by court orders resulting from litigation. We therefore identified a pressing need to collect reliable data on this matter, both to gain a better understanding of the situation and to provide inputs for a discussion of the ethical conflicts generated by current mechanisms of access to orphan drugs in Brazil—the main objective of this article.

METHODS

This was a cross-sectional, observational study approved by the Hospital de Clínicas de Porto Alegre Research Ethics Committee.

Data were obtained from various sources, such as clinical genetics services, geneticists in private practice across the country, Brazilian non-governmental organisations representing MPS patients and state health departments.

A standardised form (instrument 1; one form for each individual patient, see appendix 1) was designed for data collection and used to record the following information for each patient: date of birth, gender, state where clinical follow-up was provided, use of laronidase, and route of access to this drug (expressed as the source of funding for the drug). The following routes of access to laronidase were recorded:¹¹ (1) phase I–IV trials and trial follow-ups funded by the pharmaceutical industry; (2) expanded access programmes spontaneously funded by the pharmaceutical industry to patients not included in phase I–IV trials; (3) court-mandated funding provided by the state or federal government; (4) funding provided by the state or federal government without a court order; and (5) other types of access. Forms were sent by the research team and returned by post, email or personal delivery between January and December 2008. The listing of clinical genetics services and medical geneticists was obtained from the Brazilian Society for Medical Genetics and from the list provided in Horovitz.¹² Two non-governmental MPS I patient organisations, in the cities of Rio de Janeiro and São Paulo, were contacted, as was the Rio de Janeiro office of the manufacturer of laronidase.

A second form (instrument 2, see appendix 1) was developed to obtain data from the Department of Pharmaceutical Assistance at the Brazilian Ministry of Health Bureau of Science,

Technology and Strategic Supplies (DAF–SCTIE/MS). This form was used to gather state-specific information, with support from each state health department, on the number of MPS I patients receiving laronidase as the result of lawsuits filed against the federal or state government, and also to collect data on the same demographic variables included in instrument 1. Instrument 1 was sent directly to clinical genetics services, geneticists in private practice across the country and Brazilian non-governmental organisations representing MPS patients. Instrument 2 was sent first to DAF–SCTIE/MS, which filled out one form to serve as a model, and then forwarded this model plus other copies of instrument 2 to the state health departments (n=number of Brazilian states+federal district=27). Instrument 2 could include information on more than one patient in one single form.

Cases of MPS I both registered with and diagnosed by the MPS Brazil Network until July 2008 were also reviewed. The MPS Brazil Network is a research project funded by the CNPq, the Brazilian federal research support agency, approved by the National Research Ethics Committee (Comissão Nacional de Ética em Pesquisa, CONEP), and hosted by the Hospital de Clínicas de Porto Alegre Medical Genetics Service since 2004. The network seeks to provide diagnostic assistance, clinical support and scientific development in the field of MPS throughout Brazil. It keeps its own database and provides diagnostic testing for MPS at no cost for the patient.⁹ Registered cases were defined as all those listed in the MPS Brazil Network database, regardless of whether diagnosis was actually performed by the network; this is justified by the possibility, for instance, that a patient may have been diagnosed by a non-network laboratory (or diagnosed before 2004) but requested inclusion in the network database. Due to the small time frame analysed and considering a mean age at MPS I diagnosis in Brazil of approximately 75 months (6.5 years),¹³ as well as a median life expectancy of 11.6 years for MPS I patients,¹⁴ we presume that most patients diagnosed by the network (ie, since 2004) were alive as of September 2008.

A Microsoft Access database was constructed and data were analysed using SPSS 15.0 for Windows. The frequency of the following variables was determined: gender, age, state where clinical follow-up was provided, specific treatment and funding for current treatment.

The data obtained from the various sources mentioned above were compared and cross-checked to prevent double entry. Both instruments were designed to maintain strict patient confidentiality throughout the data collection process by identifying participants by initials alone. Variables such as gender and date of birth were used to prevent the same patient from being entered twice in the database.

RESULTS

We received 67 forms, 44 (instrument 1) from 13 attending physicians and 23 (instrument 2) from DAF–SCTIE/MS.

Five Brazilian states failed to respond to instrument 2 (sent to state departments of health). Six states reported no cases of court-mandated laronidase access.

Demographic data

After analysis and review of the data obtained and exclusion of duplicate records, we identified 68 patients with MPS I (male 34 of 66, 51.5%) alive in the study period in 15 Brazilian states and the federal district. Considering a current Brazilian population of approximately 184 million,¹⁵ the estimated minimum prevalence of MPS I in Brazil would be in the order of 1/2 700 000.

Brazil is divided into five geopolitical regions: north, northeast, midwest, southeast and south. The southeast (SE) had the highest number of patients (n=28), followed by the south (S), northeast (NE), midwest (MW) and north (N) as shown in figure 1.

Information concerning age was obtained for 92.6% (n=63/68) of cases, and most patients were younger than 15 years of age (table 1).

Routes of access to laronidase

Of the patients identified, 88.2% (n=60/68) were being treated with laronidase. In 86.6% of cases (n=52/60), access to the drug was secured through litigation against the state or federal government (table 2). Of the eight patients without treatment, three had obtained the right to receive laronidase through lawsuits; however, treatment was not being provided due to a lack of adequate facilities for infusion. Taking these cases into consideration, the rate of court-mandated access to laronidase was 87.3% (55/63).

DISCUSSION

Several scientific, political, ethical and economic aspects of orphan drug access have been discussed in developed countries, which have generally taken a favourable though cautious stance towards public funding of laronidase.^{3 16 17} Difficulties in assessing the clinical efficacy (due to the small number of patients and the impossibility of conducting adequately designed clinical trials) and cost-effectiveness of these drugs have been reported, particularly when no other treatments are available.^{3 16–18} Ethical conflicts are chiefly associated with the public funding of high-cost drugs in the light of cost-effectiveness concerns and with the need to provide care for minority groups affected by rare and severe diseases.

The sample included in the present study represents approximately 90% (68/73) of MPS I diagnosed by the MPS Brazil Network between April 2004 and July 2008, and even exceeded the number of Brazilian MPS I patients included in the MPS I Registry as of 2007 (n=29).¹⁹ The MPS I Registry is a multicentre, multinational, observational study of a broad sample of living and deceased MPS I patients that seeks to track the natural history and outcomes of these patients in order to expand knowledge of the disease and facilitate evidence-based decision-making on best

Table 1 Distribution of Brazilian patients with MPS I according to age (n=63/68)

Age (years)	No of patients	%
0–5	15	23.8
5–10	15	23.8
10–15	14	22.2
15–20	6	9.5
20–30	7	11.1
30–40	5	9.9
>40	1	1.6
Total	63	100.0

MPS I, mucopolysaccharidosis type I.

practices for monitoring and treatment of people affected by MPS I.¹⁹ Based on this information, our study sample is perfectly satisfactory in terms of representativeness, although it most certainly did not correspond to 100% of the living Brazilian MPS I population at the time of the study. The prevalence we obtained would thus correspond to the minimum prevalence of MPS I patients in Brazil. Remarkably, only 13 attending physicians replied to questionnaire 1; in the authors' opinion, this is not indicative of a low response rate, but rather shows the highly centralised nature of MPS I treatment in Brazil.

Although the epidemiological data available from the international literature concerning MPS I refer to the incidence of this disorder,² a comparison with data from the present study suggests that MPS I is either underdiagnosed in Brazil or is less prevalent than in other countries. Underdiagnosis appears more likely. The northeast and north, for instance, appear to be underrepresented in the study sample. Furthermore, as noted above, the mean age of Brazilian MPS I patients at diagnosis is higher than elsewhere. The higher prevalence in the southeast and south regions could be explained by the fact that these are the most populated regions in the country, as well as those with the highest number of specialised medical genetics services and centres,¹⁰ and therefore allow easier access to diagnosis.

The higher prevalence in patients up to 15 years of age (68.7%) suggests that the Brazilian population with MPS I is essentially paediatric and predominantly composed of patients with the severe and moderate forms of the disease, characterised by degenerative manifestations and low life expectancy.^{13 14}

Figure 1 Distribution of Brazilian mucopolysaccharidosis type I (MPS I) patients according to region and state where clinical follow-up was provided (n=68). Population data for each region were obtained from IBGE, 2007. Northeast: states of Maranhão, Piauí, Ceará, Rio Grande do Norte, Paraíba, Pernambuco, Alagoas, Sergipe and Bahia. Southeast: Espírito Santo, Rio de Janeiro, Minas Gerais and São Paulo. South: Paraná, Santa Catarina and Rio Grande do Sul. Midwest: Mato Grosso do Sul, Goiás, Distrito Federal, Tocantins and Mato Grosso. North: Pará, Amapá, Amazonas, Roraima, Acre and Rondônia.

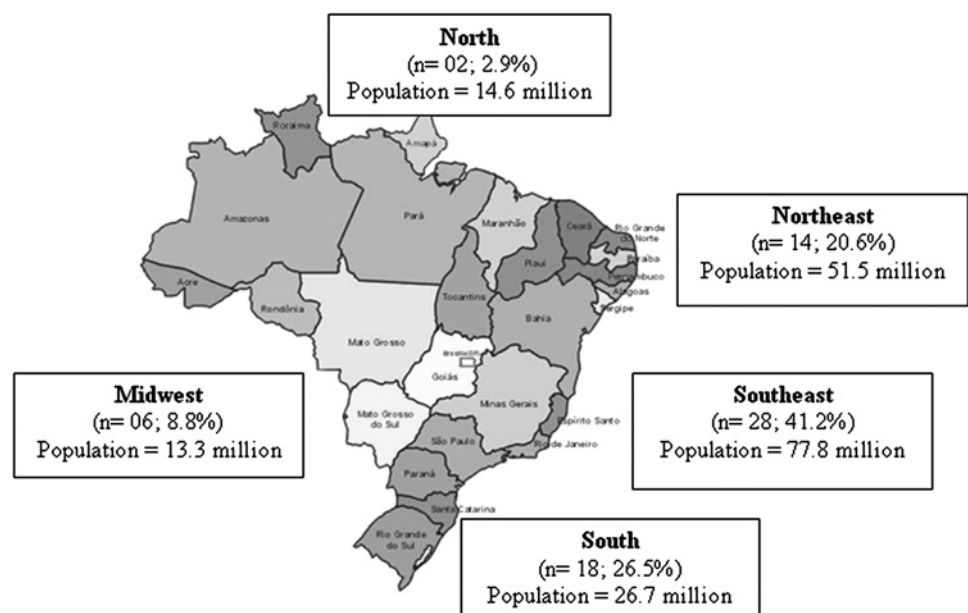


Table 2 Routes of access to laronidase according to state where clinical follow-up was provided*

State	Patients treated with laronidase (n)	Judicial access (n)	Expanded access (n)	Funded by state government (without lawsuit) (n)	Funded by healthcare plan (n)	Clinical trial (n)
Rio Grande do Sul	04	01	02	—	—	01
Santa Catarina	05	04	01	—	—	—
Paraná	05	05	—	—	—	—
Rio de Janeiro	02	01	01	—	—	—
São Paulo	12	11	01	—	—	—
Espírito Santo	01	—	—	01	—	—
Minas Gerais	09	09	—	—	—	—
Ceará	04	04	—	—	—	—
Bahia	03	03	—	—	—	—
Pernambuco	02	02	—	—	—	—
Sergipe	01	01	—	—	—	—
Rio Grande do Norte	01	01	—	—	—	—
Maranhão	03	03	—	—	—	—
Pará	02	01	—	—	01	—
Distrito Federal	04	04	—	—	—	—
Goiás	02	02	—	—	—	—
Total	60	52	05	01	01	01

*There were no reports of patients receiving laronidase in the states not listed.

These data show that diagnosed patients are at a developmental disadvantage, as they are affected by a severe chronic illness that deprives them of the prospect of a normal life expectancy. The authors also believe that milder presentations of MPS I are underdiagnosed in the country.

The vast majority of patients secure access to laronidase through the courts, not through state-funded pharmaceutical care programmes.

The judicialisation of health care in Brazil

The key argument of lawsuits seeking to ensure access to orphan drugs in Brazil is based on the following principle enshrined in the Brazilian constitution:²⁰ 'Health is a right of all people and a duty of the State, shall be guaranteed by means of social and economic policies aimed at reducing the risk of illness and providing universal and equal access to actions and services for its promotion, protection and recovery.' This fundamental principle places on the state the obligation to ensure that health care is provided in a universal, comprehensive and equitable manner by the Brazilian Unified Health System (SUS). When the government fails to provide access to any healthcare service, such as hospital admissions or diagnostic or therapeutic interventions, Brazilian citizens have increasingly sought to ensure this access through the courts. This is a growing phenomenon in the national context, especially when high-cost treatments or treatments not covered by official Ministry of Health pharmaceutical care programmes are involved.

Even when the possibility of pharmaceutical industry influence is factored into the equation, the frequency of court-mandated access to laronidase shows that the government is neglecting an unmet healthcare need of this particular patient population. Judicial interference in pharmaceutical care in this setting would therefore play a role in encouraging the implementation of public policies to ensure compliance with constitutionally mandated rules and citizens' rights, including those of segments of the population that have little bargaining power in traditional political spheres, thus preventing a 'tyranny of the majority'.²¹

However, the use of litigation to ensure the provision of constitutional benefits in an attempt to extend pharmaceutical care to all those who require it may have several negative consequences, such as budgetary imbalances, an increase in the irrational use of public financial resources, compromising equity;

and distortions in the national drug policy,²² even if it is poorly equipped to meet current technological advances. This is because court orders force purchase of the drug before procedures such as government authorisation for procurement and distribution of the drug are begun, and before clinical protocols and therapeutic guidelines have been developed and specialised centres of excellence have been defined to handle administration and follow-up.

The three cases in which laronidase was judicially obtained but not used due to the lack of an appropriate facility for administration (laronidase is given exclusively by the intravenous route, and is best administered in a hospital setting) reflect a distortion in the process of granting access to the drug, and reveal a need for creating new facilities to reduce inequalities in access to specialised treatment centres. This situation jeopardises the principle of comprehensive coverage (providing access to all required treatments at all complexity levels) as defined by SUS, which advocates the use of all necessary means to provide care at the appropriate level of complexity.²³

There is a need to guarantee the right to health care, as expressed in article 196 of the Brazilian constitution. However, Brazil does not have a well-defined public policy for the use and funding of orphan drugs. A resolution has recently been issued that makes a distinction between 'neglected diseases' and 'rare or orphan diseases', defined as 'those affecting a small number of people as compared to the overall population'.²⁴ The WHO defines neglected diseases as those associated with poverty, poor living conditions and health inequalities. Although neglected diseases account for nearly half of the total burden of disease in developing nations, research and development funding has traditionally not prioritised this area. There is no commercial interest to develop drugs for the treatment of neglected diseases, as they provide no potential of profitability; pharmaceutical manufacturers are more concerned with patenting high-cost drugs, such as those used in the treatment of orphan diseases.¹⁶

Even though some orphan drugs are already marketed in the European Union, in the USA, Australia and some Asian countries,⁵ only a few such medications have been included in the Brazilian Ministry of Health list of drugs for the treatment of rare disorders. One example is imiglucerase, a recombinant enzyme used in the treatment of Gaucher disease. Gaucher disease is a rare lysosomal storage disorder associated with organomegaly, bone changes and, in some forms, neurological

involvement. Efficacy and cost-effectiveness data are available for imiglucerase as a treatment for non-neuropathic type Gaucher disease, and clinical protocols for its use have been outlined.^{25 26} In turn, the non-inclusion of laronidase in the specialised drugs list may have several explanations, namely: (1) the unavailability of research; (2) the scarcity of evidence of effectiveness;^{27 28} and the fact that (3) benefit has been observed only for specific groups of MPS I patients.^{8 28 29}

Concerns with public funding for orphan drugs are by no means recent. Even in developed countries, public funding of laronidase treatment and therapy with other orphan drugs has been the subject of discussion; the European Union, for instance, has no single, unified orphan drug policy for its member states, which show extensive variability in types and routes of access to available orphan medications. Countries such as the UK, Australia and New Zealand, in addition to using different criteria for the public funding of drugs, also include estimates of clinical effectiveness and cost-effectiveness.^{30 31}

Considering that orphan drugs have not shown cost-effectiveness when analysed with criteria and methods currently used to assess the incorporation of health technologies, but have nonetheless been approved for use in many countries, economic criteria have clearly not proved sufficient for decision-making. Each country must thus face the challenge of developing its own policy for funding these drugs.^{3 31}

Ethical conflicts

The principlism model of bioethics upheld by Beauchamp and Childress³² views biomedical ethics as the application of general ethical principles to the issues of medical care and practice. Of the four principles on which the model is based—autonomy, beneficence, maleficence and justice—the latter is most relevant to the subject of this article. Health-related inequalities are wide-ranging in Brazil, and are by no means restricted to orphan diseases. The universal healthcare system is not only deficient in the extent to which it meets the normal demands of the population, but is also plagued with severe issues regarding the management of available resources. To make matters worse, the SUS is staunchly defended as a near-sacred accomplishment; campaigns are underway to have it granted intangible cultural heritage status. This means that, due to ideological constraints, discussion of the main source of conflict in the case of orphan drugs (targeting vs universalism) is simply impossible. Equitable principles, such as those underpinning the SUS framework, require that resources be equally distributed to all. However, analysis of the needs of specific populations—in this particular case, patients with severe rare diseases—shows that, paradoxically, these equality policies do not translate to actual practice. The system is at once egalitarian and exclusive, as it fails to include all patients who require its support. Despite this finding, there is no discussion of the need for targeting groups that should be ensured access to the state health system in Brazil.

Assuming that all human beings are equal in the eyes of the law, the only fair distribution of health care is an equal one, but a closer look at the subject of this article shows that this purported equality has not come to fruition. To obtain access, patients must go through the courts, which, in Brazil at least, rule in favour of the plaintiff in nearly 100% of cases. The arguments mentioned by judges in their rulings are predominantly based on the aforementioned constitutional principle (right to health) and on the right to life.

In his *Theory of justice*, Rawls³³ sets forth the idea of the 'veil of ignorance': only by not knowing one's own place and prospects in society (and those of others) can one comply with the principles

of justice, which he reduces to two: the principle of equal liberty and the difference principle, which ensures that, if inequality occurs, it will be of the greatest benefit to those worse off. The theory of justice as equity conveys the notion that the principles of justice are agreed upon in an original equitative position.

Daniels³⁴ carries Rawls' considerations into the field of health care, based on the principle of 'equitative equality of opportunity' as the only way of meeting the need for fair medical care. Discussing Daniels' principle, Beauchamp and Childress³² note that the elimination of barriers that prevent equal opportunity access is an obligation of society, including programmes aimed at correcting or compensating for various types of disadvantages. Daniels views disease and disability as unwarranted restrictions that deprive individuals of the opportunity of having basic needs met. From this standpoint, the only way of ensuring justice would be to allocate health resources in a way that provides for equitative equality of opportunities.

We must also note the situation described by Sen,³⁵ in which individuals are denied a basic 'freedom of development' (access to health care) due to their social and/or economic status. From this standpoint, we ask ourselves whether it would not be morally acceptable for the state to provide access to orphan drugs, in an attempt to eliminate the restrictions that limit the choices of these individuals and their opportunities for acting on their own behalf and building their own future according to their hopes and wishes. Our finding that MPS I is a predominantly paediatric condition could constitute an even more compelling moral argument in favour of this approach, in light of the early age at which patients with this disease are deprived of their capabilities.

Both the concept of equity as expressed by Rawls and Daniels and the notion of capabilities set forth by Sen implies that the social distribution of resources must be arranged in such a way as to decrease or eliminate unfair resource allocation, thus giving people with disease and disability the opportunity of developing as far as those not affected by these restrictions. The concept of equitative opportunity may be summarised as follows: no social benefits should be granted on the basis of unwarranted or undeserved favourable circumstances, and no benefits should be denied on the basis of unwarranted or undeserved unfavourable circumstances. As noted by Beauchamp and Childress,³² discrimination based on social and biological attributes acquired involuntarily at birth is unacceptable.

People with disabilities are the target of myriad biases, prejudice and discrimination. Some believe they should not be born at all, and maintain that it would not be wrong to leave them to die, as they would not live long anyway and are unable to bring happiness to themselves, their families, society, or the state.³⁶ Employing limited resources to meet the needs of a minority would be tantamount to stealing resources meant to meet the needs of the majority. This is the main utilitarian argument against public funding of orphan drugs: it would be unethical to invest substantial resources towards the treatment of rare conditions, which does not bring maximal benefit to society, when equally serious issues (such as neglected tropical diseases) affect a much larger segment of the population, especially in developing countries.¹⁶

On the other hand, under the principle of beneficence,³² society would be morally obligated to provide these medications to individuals who have had the misfortune of being born with a severe disorder, however few these individuals may be. To do otherwise would constitute abandonment of individuals who require highly specialised medical services, even when scarce resources are a concern.¹⁶ Denying funding of orphan drugs has therefore become politically problematical.³¹

The rule of equitable opportunities, as applied to health care, mandates the rejection of policies that deprive people with rare diseases of available therapies simply because these are costly. Decisions on which drugs to cover will ultimately depend on the political and social acceptability of denying (or providing) access,³¹ taking into account economic and moral aspects alike. The need for technical criteria to determine the actual benefits of orphan drug use is also a challenge that must be faced, as are cost-effectiveness issues.³⁰ The best approach may be one based on deliberative democracy, in which society at large (and groups affected by the issue in particular) are heard openly and in an environment conducive to negotiation, leading to well-founded, rational decisions on orphan drug access, rather than the current scenario of court-mandated funding. A representative survey of public opinions on orphan drug funding, including priority space for minorities, should be the subject of future studies.

CONCLUSION

The data presented above show that, despite the small number of MPS I patients diagnosed and treated in Brazil, the country is in dire need of public policies to help plan for (and meet) the growing demand for novel pharmaceutical treatments of other genetic conditions.

By stressing the rule of equitable opportunities, we sought to point out the possibility that healthcare policies and practices that have 'meets the needs of the majority' as the sole criterion for allocating medical services can produce discriminatory impacts. As noted by Beauchamp and Childress,³² public policies should usually include moral considerations; ethical analysis must therefore be a key part of policymaking, not a means of assessing existing policies.

We therefore conclude that benefits cannot be denied on the basis of unwarranted, unfavourable conditions—such as being affected by a genetic disorder. Equal access and equal opportunity are accepted as ethical values by most thinkers—and it is this ethical principle that is being fulfilled by proposals aimed at saving lives or preventing damage. It is therefore necessary to change both the standpoint according to which the issue is addressed and the operational framework of services that do not currently prioritise this segment of the population. The fact that other variables must be taken into account stresses the need for an ethical outlook in the development of a healthcare programme targeting patients with genetic disorders in general, not only MPS I, as the concept of ethics is defined by a concern with others.

We hope the case of MPS I in Brazil can be an example to broaden the discussion of orphan drug access and similar issues, helping to bridging the gap between universal healthcare access and patients affected by rare diseases and outline solutions for ethical issues generated by the disconnect between the constitutional right to universal health care and the reality of deficient resources.

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APPENDIX 1

Instrument 1

Date: _____
 Name of person completing form: _____

Patient (initials only, please): _____

Date of birth: _____

Gender: _____

Place of birth: _____

State where treated/monitored: _____

Current weight: _____

CURRENT TREATMENT:

- Is the patient CURRENTLY receiving any disease-specific treatment?
 no
 yes. Which treatment? (Include start date and, if enzyme replacement therapy, product name)

- This treatment was **initially** funded or guaranteed by:

- a Phase II clinical trial
 a Phase III clinical trial
 a postmarketing study
 a manufacturer-funded expanded access program
 a court order (state government as defendant)
 the state government (no court order necessary)
 the federal government (no court order necessary)
 other (please specify):

- This treatment is **currently** funded or guaranteed by:

- a Phase II clinical trial
 a Phase III clinical trial
 a postmarketing study
 a manufacturer-funded expanded access program
 a court order (state government as defendant)
 a court order (federal government as defendant)
 the state government (no court order necessary)
 the federal government (no court order necessary)
 other (please specify):

PRIOR TREATMENT (other than that described above):

- Has the patient received any disease-specific therapy IN THE PAST?
 no
 yes. Which therapy? (Include start and end dates, and, if enzyme replacement therapy, product name)

- This treatment was **initially** funded or guaranteed by:

- a Phase II clinical trial
 a Phase III clinical trial
 a postmarketing study
 a manufacturer-funded expanded access program
 a court order (state government as defendant)
 a court order (federal government as defendant)
 the state government (no court order necessary)
 other (please specify):

Instrument 2

Please fill out the following form for all patients with MPS I currently receiving State Government/State Department of Health-funded enzyme replacement therapy (use additional sheets if necessary)

Date: _____

Name of person completing form: _____

Patient (initials only, please): _____

Date of birth: _____

Gender: _____

Place of birth: _____

State: _____

Patient (initials only, please): _____

Date of birth: _____

Gender: _____

Place of birth: _____

State: _____

Patient (initials only, please): _____

Date of birth: _____

Gender: _____

Place of birth: _____

State: _____

Patient (initials only, please): _____

Date of birth: _____

Gender: _____

Place of birth: _____

State: _____



Ethical issues related to the access to orphan drugs in Brazil: the case of mucopolysaccharidosis type I

Raquel Boy, Ida V D Schwartz, Bárbara C Krug, et al.

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