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RARE DISEASES ORPHAN DRUGS

Official Newsletter of the Bulgarian Association for Promotion of Education and Science (BAPES)

FOCUS ON:
WHAT IS OFFERING THE HEALTH TECHNOLOGY ASSESSMENT TO RARE DISEASES AND ORPHAN DRUGS?

Dear friends,

The December issue of "Rare Diseases & Orphan drugs" always has a special emotional charge for many reasons.

Those of you, who follow us from the very beginning, probably remember that just two years ago, on December 10, 2010 our first issue came out. For these two years the newsletter has undergone major transformations, but we are now even more strongly convinced in the power of information and the need for our small but growing community to be aware of the latest news and to be able to quickly communicate within itself and its members. Thank you for your trust and support, that you give us every time you access the web or PDF version of the newsletter. This is our greatest reward and incentive for further work.

Of course, December is a time of bright holidays, family atmosphere and warmth. The team of "Rare Diseases & Orphan drugs" wishes you a merry Christmas and a happy, healthy and successful New Year of 2013! Let us all be more ambitious and principled next year to realise our shared dream of a better, fairer and more responsible society. We count on each of you!

The new issue presents interesting and useful information on the developments in the field of rare diseases. It is introducing in detail the concept of health technology assessment and the expected benefits for rare diseases and orphan drugs stakeholders. Two leading experts on this issue – Dr. Edmund Jessop and Ms. Jacqueline Bowman will speak about their experience and views. "Rare Diseases Library" features an overview of a rare disease called Friedrich ataxia. And now, let's start by pointing out the most important moments of the past year.

HAPPY HOLIDAYS WITH "RARE DISEASES & ORPHAN DRUGS"!

RARE DISEASES AND ORPHAN DRUGS IN 2012

What you should not miss

IN BULGARIA

☑ 3RD NATIONAL CONFERENCE FOR RARE DISEASES AND ORPHAN DRUGS

☑ EMPOWERMENT OF RARE DISEASES PATIENT COMMUNITY IN BULGARIA

☑ PROVISION OF TREATMENT FOR MUCOPOLYSACCHARIDOSIS PATIENTS

☑ TOWARDS HEALTH TECHNOLOGY ASSESSMENT

RARE DISEASES AND ORPHAN DRUGS IN 2012

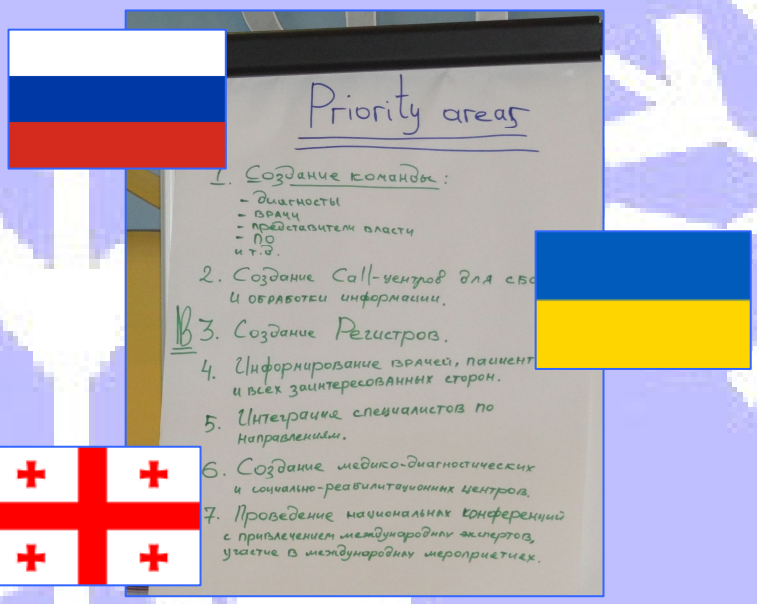
What you should not miss

IN EUROPE AND AROUND THE WORLD

☑ **INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM (IRDiRC)**

☑ **NEW EU REGULATIONS**

☑ **PROGRESS IN EASTERN EUROPE**



☑ **8 NEW MARKET APPROVED ORPHAN DRUGS**

☑ **BREAKTHROUGH IN GENE THERAPY**

WHAT IS OFFERING THE HEALTH TECHNOLOGY ASSESSMENT TO RARE DISEASES AND ORPHAN DRUGS?

Improving the population's health status is associated with the strengthened ability to predict, prevent, diagnose and treat many diseases, as well as with the implementation of procedures and the use of technologies that we could hardly imagine some decades ago. Health technologies are essential for the health system's functional capacity. Last month we witnessed a series of discussions in the National Assembly on the concept of health technology assessment (HTA). The first of these sessions was dedicated to the application of this new discipline to the field of rare diseases and orphan drugs. Can we expect a significant effect upon the future implementation of HTA in Bulgaria and how this process should be managed to allow doctors and patients to experience maximum benefits?

The term "health technology assessment" means any process of examination and report on the properties of medical technologies used in health care – safety, efficacy, administration, indications and instruction for use, cost effectiveness, social, economic and ethical implications. Many of you may immediately ask if HTA is already performed in our country. The answer is yes and no in the same time.

Each drug or medical device is examined in one way or another when applying for import permit, pricing or deciding on possible reimbursement from public funds. However, this is not HTA in the full sense of the term. HTA is not legally defined in the country and all cited procedures are largely independent of each other, sometimes repetitive, sometimes even competitive. Besides, this evaluation is not complete – it usually comes down to review the results of clinical studies and to check the financial projections for the technology's use. HTA requires much more – this should take into account effectiveness, efficiency and most importantly – consequences. Last but not least, in addition to the lack of HTA legal and institutional framework, there is also no expertise to conduct such a comprehensive assessment in Bulgaria.

What would bring the application of this methodology in Bulgaria? The need for HTA has been first recognised back in mid 60s of the last century, prompted by awareness of the critical role of technology for today's society and the potential unintended and sometimes harmful consequences of its use. The large experience with side effects has contributed to consider this apprehension a necessity. This evaluation was greatly designed as a way to identify the results expected from the use of a technology, but more importantly – the unforeseen social, economic and environmental consequences too.

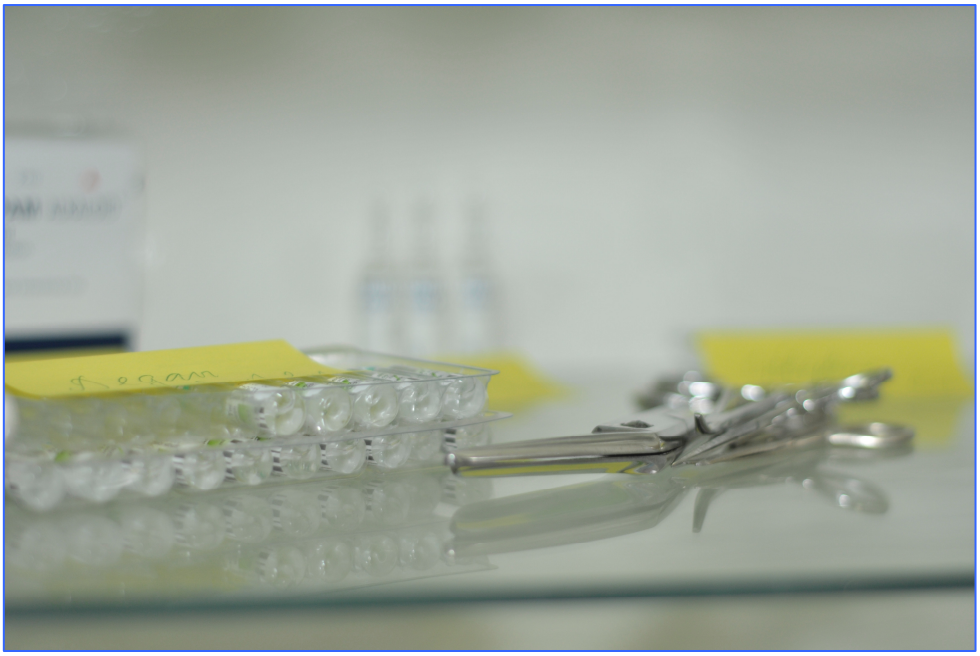
Today, HTA concepts receive wide application due to their primary function of being a reliable tool for the allocation of limited resources in face of growing needs. This paradigm has emerged as a logical response to the concerns of decision-makes about the uncontrolled proliferation of expensive medical technologies. An early example of HTA is from 1970s, when the growing demand for CT had become a public issue because of the very high unit price at this time. HTA is offering to the policy makers and decision takers a set of analysed policy options with description of their effects on economic, environmental, social, political and legal

processes, as well as their influence on public institutions. The purpose of HTA is to provide information on the possible alternatives. This mission is critical, especially now in the time of economic crisis.

Where is the particular position of rare diseases and orphan drugs in HTA? Health technologies include any technology used to save lives of individuals from a wide range of risks and diseases. Currently, the medicine is using more than 500 000 medical technologies and they all share a single goal – improving and extending lives. The common thread to the application of all is the health gain and quality of life. They all empower individuals to contribute longer for the society's prosperity. Quality of care, efficiency and sustainability of health systems are enhanced.

Some health technologies, such as plasters, syringes and latex gloves are well known and routinely used every day. Glasses, wheelchairs and hearing aids are also in this category. Roughly speaking, these are relatively inexpensive technologies, their effects and benefits are well acknowledged and they are regularly prescribed to a large number of people. Innovative advanced health technologies, like full-body scanners, heart pacemakers, hip joint replacements are however the opposite case. The vast majority of therapeutic approaches for rare diseases are also here. The common denominator between them is the high cost, innovative character and relatively recent marketing. These are not simple procedures and their application requires significant experience and knowledge. And not only. They demand a more detailed and careful consideration, because their effects are not yet fully clear. A careful justification for allocating resources to acquire and use them is needed.

Rare diseases and orphan drugs have an extra burden – the rarity. The fact, that a technology is designed for a limited number of people, makes the process of assessment much more complicated, and the results are not always obvious.



First, rare diseases' etiology is not yet fully understood, a major challenge is to diagnose most of them. The small number of patients means it is more difficult to conduct clinical trials for new health technologies. Unlike common disorders, once rare diseases therapies get to the stage of market authorisation, they do not have a solid and comprehensive evidence data. This uncertainty is a big obstacle to get them covered by public funds. Policy makers and health insurers have the task to manage healthcare funds in a reasonable manner. Nobody wants to take the risk of a technology whose effects and implications are unclear. Patients themselves are also being suspicious of such therapies.

Of course, the financial element should not be forgotten. Research and development of new therapies for rare diseases is a complex and risky process that lasts for years and takes many human and material resources. Once a successful outcome is produced, pharmaceutical companies have little time left before the technology lose patent protection and become open for other producers. That is why the most normal thing in this period is to seek covering scientific research and development expenses. However, brought to a very small number of end-users, these new therapeutic approaches are proving to be extremely expensive, even for high-income countries. Thus, these new technologies could be available and accessible to patients only if government takes over their provision. But public health authorities everywhere have to deal with limited budgets. Finding a solution leads to the application of the criterion of cost-effectiveness where rare diseases experince a kind of discrimination. Not being accessible, innovative therapies can not generate sufficient information on their clinical effect. Orphan drugs come to a situation in which they do not show significant clinical benefit in practice and their price is very high. So, they can not cover any conditions for cost efficiency and subsequently they are rejected for reimbursement.

HTA can help in dealing with these "embedded" shortcomings of rare diseases and orphan drugs. It has a complex character and it is not just about the traditional clinical effectiveness and price. It takes into account the social and economic impact on society, specifics of the disease and the affected group, innovative nature of the technology, social attitudes, principles of equality, solidarity and non-discrimination. All this combined reveals the enormous added value of rare diseases and orphan drugs. Rare diseases have shown a huge role in fostering the potential of research and development activities. Major advances in rare diseases diagnosis and treatment have proved that anything is possible. Moreover, many of these breakthroughs then served for a number of findings for common and socially significant diseases. It is important to consider the enourmous socio-economic burden that people with rare diseases and their families carry, this means huge losses, both in economic and human potential aspects.

In a conclusion, properly assessed and appropriately used, new health technologies for rare diseases could bring many benefits to everyone, not only for rare diseases stakeholders. Rare diseases and orphan drugs are able to generate enormous added value for all and in many different ways. They only need to be given a chance to prove in practice!

IN A TIME OF ECONOMIC DIFFICULTY

SOME FORM OF HEALTH TECHNOLOGY APPRAISAL IS INEVITABLE

Health technology assessment is a relatively new concept not only in Bulgaria but worldwide. That is why we have decided to invite two renowned international experts to present in detail the challenges of this process. They have another great advantage – both have worked for years in the field of rare diseases. They are best able to highlight the benefits to patients and physicians from the application of health technology assessment.

Our team takes this opportunity to thank Dr. Edmund Jesop and Ms. Jacqueline Bowman for their sincere support!

May you briefly introduce yourself to our readers?

Edmund Jessop (EJ): My name is Edmund Jessop. I am medical adviser to the Advisory Group for National Specialised Services. Our team plans, funds, and monitors a set of services for very rare and highly specialised services provided by the National Health Service in England.

Jacqueline Bowman (JB): I am the Executive Director of EPPOSI (European Platform for Patients' Organisations, Science & Industry) which is a think tank active on addressing questions on health policies at a European level that aim to bridge the gap between innovations and improved health outcomes of citizens. We have been in existence since 1994 and now have 55 member organisations equally weighted between representatives from patients organisations, science, academia, research and various industry sectors (pharmaceutical, diagnostics), including Eurordis and EGAN as well as ESHG, all key actors within the rare diseases field in Europe.

Dr. Edmund Jessop

First of all, is there a particular reason for you to be involved in rare diseases activities? When did you first "face" the rare diseases?

EJ: I have been working in this field since 2002. I am involved because the work is both enjoyable and rewarding. It is enjoyable because all of the many clinicians and patient organisations I work with are enthusiasts who are dedicated and hard working. It is rewarding because many of the conditions we deal with are devastating in the their effect. Many are untreatable but over the years we have seen enough improvement in some diseases to give hope for everyone.

JB: When EPPOSI started as an organisation, the main area of activity was rare diseases and EU legislation. Joining in 2010, I have been very keen to continue that tradition because there is still very much a clear need for different stakeholders to find solutions together.

On a personal note, I am sickle cell trait, with low level symptoms of a sufferer. Various people in my family have died unnecessarily from this rare condition due to lack of awareness and access to medication. Anything that I can do to support finding solutions is very much welcomed.

HTA is already an internationally recognised field for specific activities and cooperation. In Bulgaria, however, this issue has been only recently discovered. What is the HTA added value for the health system and society in general?

EJ: The National Health Service in England was one of the first to adopt health technology assessment systematically, by setting up the National Institute for Clinical Excellence (NICE). NICE has been portrayed in the press as an organisation which denies treatments for patients but its original aim was exactly the opposite – to ensure that payers did not, throughout ignorance, refuse funding for effective new treatments. In a time of economic difficulty some form of health technology appraisal is inevitable.

Some treatments will be very expensive and achieve little; others looks expensive but actually bring years of added benefit to patients and so work out cheap You need to know that you are getting the best possible health gain from the money you spend. HTA answers two fundamental questions: what does this cost? And how much good does it do?

JB: HTA is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased robust manner. It aims to inform the formulation of safe, effective, health policies that are patient-focused and seek to achieve best value. If HTA is correctly carried out it could encourage innovation; become a bridge between the all different stakeholders involved; optimise the use of healthcare resources; conduct efficient cost-effectiveness and clinical-effectiveness reports; draft efficient policy recommendations; maximise patient outcomes.

In recent years, HTA processes have turned their focus beyond that of purely cost-effectiveness and strive for consideration of ethical, organizational, social issues and patient involvement, since patient defined outcomes are vital for HTA. Especially for rare diseases though, we need to ensure a transparent and close collaboration between all the stakeholders involved in order for HTA to be flexible and a wide societal perspective with patient needs at the core, which will provide equity of access to all patients with rare diseases. This will be the real added value of HTA.

You have a wide perspective on HTA organisation and methodology. What lessons could you recommend for a country in transition like Bulgaria?

EJ: HTA is a powerful tool which helps to avoid erratic decision making. The basic concepts are easy to apply but a full HTA takes time and costs money; there are not many teams which can do it well. So choosing which drugs and treatment to submit to HTA is itself a decision. You need to decide whether to start with common conditions or rare, with existing treatments or new, with drugs only or all treatments.

JB: Each HTA system depends on the setting in which the organisation operates, the existing funding, the types and scope of assessments conducted by the organizations, the activities other than the production of HTA reports and their relationship to decision-making. Bulgaria is in a very advantageous position because you are at the stage of being able to build an HTA system taking best practices from other European countries that have had to create through trial and error. You have the opportunity to take society's views and needs into account when setting up the HTA system and not only looking at short terms gains for a very limited health system budget when only considering cost effectiveness.

EPPOSI has been working on a framework for a more inclusive approach for HTA processes which will significantly benefit the rare disease community and society in general. According to the EPPOSI research and stakeholder consensus, a societal benefits approach to HTA means a process that involves principles of solidarity, transparency, equality and effectiveness, where the involvement of all stakeholders plays a crucial role and can be achieved by better targeted use of monetary and non-monetary resources across relevant policy sectors. The scope of societal benefits in HTA includes a clear ethical aspect that extends to the inclusion of workability and the quality of life of patients, families and care-givers in the framework.The main principles revolve around value, governance (solidarity, transparency, equality), all stakeholder involvement, stakeholder/patient-defined outcomes, psychological aspects, workability/continued economic activity, ethical aspects, cross-sectoral policy making.

As we conduct a study ourselves centered on the societal benefits approach of HTA we have noticed that in many countries, their HTA system has a lack of ethical aspects or of the patient empowerment or transparent and consistent governance needed along with all stakeholder involvement. Our goal is to build a multi-stakeholder framework for a societal benefits approach to HTA, focusing on how to effect attitudinal as well as systemic change in HTA structures and processes, which can take better account of smaller, specific patient groups across Europe, as well as the needs of wider populations. Bulgaria, being a country in transition, could benefit from our societal benefits approach, since a lack of societal perspective, especially for rare diseases is the missing gap on the standard HTA procedures.

Talking about rare diseases and orphan drugs, what is the role of HTA in this sphere?

EJ: Many orphan drugs are for cancer; HTA works well in this field. Difficulties arise when you want to use HTA for lifelong conditions, because you have to extrapolate results from 18 months of treatment in a trial out to a lifetime of 10, 20 or 30 years. Furthermore you have to extrapolate from measures of function (such as the 6-minute walk test) to expected survival and to quality of life. Those extrapolations are very imprecise and so the whole HTA becomes imprecise.

It is also true that for very rare or 'ultra rare' disease (with a prevalence of 1 in 100 000 or fewer)' the treatments tend to be very expensive. This is not a limitation of the HTA but it does pose problems for decision makers. In the UK we have separate decision systems for ultra rare conditions. The HTA is the same, but the funding decision is made using a different set of criteria.

Jacqueline Bowman
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JB: Standard HTA procedures evaluate cost-effectiveness and clinical effectiveness. However, rare diseases are not the standard HTA subject for evaluation. Rare diseases usually do not have a comparator because no alternative exists and moreover, the evidence for orphan medicines is very limited. Furthermore, patients of rare diseases represent a very small percentage and orphan drugs are too expensive to meet the standard cost effectiveness threshold. On all these grounds, conventional HTA methodologies risk denying patients access to potentially life-saving orphan drugs. Therefore, HTA bodies need to broaden the range of criteria they consider in their assessments if these patients are to avoid being left behind. If we look at the AGNSS case, it is an interesting example of rare diseases and orphan drugs HTA and we could learn lessons from the MCDA (multi-criteria-decision-analysis) approach used, since it covers a wide societal perspective. AGNSS is the Advisory Group for National Specialised Services. It offers a new HTA methodology for Ultra orphan drugs and provides a single source of advice to Ministers on which services at which centres should be nationally commissioned, as well as a small number of highly specialised new drugs and technologies that are not suitable for consideration by NICE.

MCDA in HTA is an analytical framework that systematically considers additional criteria beyond cost effectiveness, such as societal preferences, equity and benefits to caregivers, disease rarity and severity, availability of alternative health technologies, impact of drug on disease, single or multiple indications, clinical evidence, and manufacturing complexity. This method avoids the use of QALYs-which is unsuitable for rare diseases due to their high cost and lack of alternative treatments-, it allows flexibility, it focuses on the patient need and patient empowerment. It provides all stakeholder involvement, provides support to patients and their caregivers and allows further data collection, since data for rare diseases and orphan drugs is difficult to find or generate.

What's your message to "Rare Diseases & Orphan Drugs" readers?

EJ: HTA is here to stay so you need to understand how it works. It does have some limitations but be clear what those limitations are. And separate the analysis – HTA – from the decision.

JB: I see an ever growing concern for rare diseases from all over EU and new stakeholders are getting involved. This is very important, because the most essential factor is to have a stable and favourable policy and regulatory framework to incentivise development and patient access to orphan drugs. Also HTA is very useful and if we modify it in order to capture the value of rare diseases and orphan drugs, it could be a helpful tool for decision-making. The important aspect is for all stakeholders involved in HTA and decision-making to realise that rare diseases are a special category and if the HTA methodology is conducted in such a way, for instance MCDA, it would benefit patients with rare diseases. As mentioned before, MCDA reflects a more holistic and societal approach to HTA of rare diseases, which is able to capture not only the cost-effectiveness and clinical-effectiveness, but also the ethical and psychological aspects, patient-defined outcomes, transparent cross-sectoral policy, equal distribution and accessibility of treatment for all patients of rare diseases.

FRIEDREICH ATAXIA

DEFINITION AND PREVALENCE

Friedreich ataxia (FA) is an inherited disorder affecting the spinocerebellar tracts, dorsal columns, pyramidal tracts, and, to a lesser extent, the cerebellum and medulla. The progressive dammages are reflected in a series of problems with the nervous system, speech and walking. FA may induce heart disease and diabetes.

FA is the most common hereditary ataxia. It occurs with a prevalence of approximately 1 in 50 000 in Caucasian populations, but is very rare among sub-Saharan Africans and virtually does not exist in the Far East. FA affects both men and women equally. 1 in 110 is a carrier of the pathological gene.

ETIOLOGY

FA is inherited as an autosomal recessive disorder. FA is caused by mutations in the FRDA gene which encodes the protein frataxin. Frataxin is necessary for the proper functioning of mitochondria. The pathogenic mutation is an expanded GAA triplet repeat in intron one of the FRDA gene in 98% of mutant alleles. The fact that one mutation accounts for the vast majority of FA means that there is a relatively simple diagnostic test available for this disease.

The caused mitochondrial dysfunction leads to degeneration of nerve tissue in the spinal cord, in particular sensory neurons essential for directing muscle movement of the arms and legs. The spinal cord becomes thinner and nerve cells lose their myelin sheath.

DIAGNOSIS

Diagnosis is made through a thorough physical examination that may include tests for reflex and sensory responses. Laboratory tests such as the electromyogram and nerve and muscle biopsies may also be used to confirm the diagnosis. In addition, the physician may take an electrocardiogram to determine if abnormalities in the heartbeat exist, and blood and urine analyses may be made to check for diabetes.

CLINICAL PICTURE

In general the first symptoms are manifested before adolescence and include incoordination of limb movements, dysarthria, nystagmus, diminished or absent tendon reflexes, Babinski sign, impairment of position and vibratory senses, scoliosis, pes cavus, and hammer toe. The typical clinical triad of hypoactive knee and ankle jerks, signs of progressive cerebellar dysfunction, and preadolescent onset is in most cases sufficient for the diagnosis.

There are conditions associated with FA that do not result from the degeneration of nerves. Heart disease is sometimes in very severe forms. Abnormalities in heartbeat rhythm and diminished strength of the heart muscle have been noted in a large percentage of FA patients, with palpitations and dyspnea (shortness of breath) the most common found symptoms. Diabetes mellitus, characterised by abnormally high blood and urinary sugar levels, is another condition that may attend FA.

Symptoms typically begin sometime between the ages of 5 to 15 years. Their progression is slow. Lower limbs are more affected. FA usually results, within eight to ten years following the onset of symptoms, in an inability to walk. Occasionally, the disease goes into spontaneous remission, which sometimes lasts five to ten years or longer. Remissions, however, are uncommon.

TREATMENT

At present there is no generally accepted treatment for FA, all therapies are symptomatic and response to particular clinical sign.

The mitochondrial dysfunction in AF has some treatment perspectives with *idebenone*, a free-radical scavenger. This rationale is based on the fact that the frataxin gene is involved in the regulation of mitochondrial iron content. The in-vitro data have suggested that both iron chelators and antioxidant drugs, that may reduce iron, are potentially harmful in FA patients. Conversely, preliminary findings suggest that *idebenone* protects heart muscle from iron-induced injury. Clinical data are still partial as the drug is approved for use in Canada, but is still under investigation in the EU and USA.

A 4-year follow-up on 10 FA patients treated with *coenzyme Q10* and *vitamin E* showes a substantial improvement in cardiac and skeletal muscle bioenergetics and heart function. Antioxidant treatment resulted in sustained improvement in mitochondrial energy synthesis that was associated with a slowing of the progression of certain clinical features and a significant improvement in cardiac function. More recent studies direct the attention towards *L-carnitine* as a promising substance for treatment of FA patients.

Orthopedic intervention, which may include surgery, can alleviate scoliosis, and orthopedic appliances and physical therapy help prolong ambulation.

REHABILITATION AND FOLLOW-UP CARE

Physical therapy has a proven positive impact on managing the symptoms of AF. A team of neurologist and specialists in physical rehabilitation and occupational therapy prepare an individual programme tailored to the patiet's abilities and health status.

A special target of physiotherapy is maintaining the capacity to walk alone. Low-intensity strengthening exercises are included to preserve the functionality of upper and lower extremities and to prevent immobility. Fatigability should be carefully monitored. Stabilising back and waist exercises help to control posture and reduce spinal curvature. Balance and coordination training may be conducted using visual feedback. Exercise can imitate everyday activities such as moving, personal hygiene, cooking, etc. In addition, the patient should be trainined to avoid the risk of falling. A speech therapist could be also included to manage linguistic and oropharyngeal problems.

Mobility aid devices can be also considered, as they may lead to a higher degree of autonomy in some cases.

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UPCOMING RARE DISEASES CONFERENCES, WORKSHOPS AND INITIATIVES

- **17-18 January 2013 – 9th EGAN / Roche Strategy Workshop "In Times of Crisis: Sustainable Healthcare Systems and the Role of Patient Groups", Basel**
- **4 February 2013 – EPPOSI Workshop "Building a Framework for Societal Benefits Approach to Health Technology Assessment", Brussels**
- **28 February 2013 – 6TH Rare Disease Day**
- **16-17 April 2013 – 1st International Rare Diseases Research Consortium (IRDiRC) Conference, Dublin**
- **13-14 September 2013 – 4th National Conference for Rare Diseases and Orphan Drugs, Plovdiv**

CHARITY CALENDAR "TOGETHER AGAINST THE DISEASE"

For a second consecutive year, the National Alliance of People with Rare Diseases is releasing a charity calendar. While last year's initiative presented young patients with rare diseases, this year six beautiful Bulgarian women with rare diseases stand up to show that life can be good despite the disorder. The "beautiful faces" of rare diseases want to encourage all patients, who feel lonely and isolated, to continue to fight for their life and to aim to realise their potential, despite prognosis and difficulties.

Proceeds from the calendar will be used to purchase oxygen masks for patients with cystic fibrosis.

To find out more, please contact the National Alliance of People with Rare Diseases (e-mail nahrb.varna@abv.bg, phone +359 889 324 216, Ms. Vania Dobreva).

Editorial Box

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