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COMMENTARY

Rarer dementias, limited options, and unaddressed needs

Commentary on "A Mixed Methods Evaluation of a Programme Exploring Pre-death Grief and Loss for Carers of People with Rarer Dementias," by Stevens-Neck *et al.*

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Rarer dementias, as featured in a paper in this issue of *International Psychogeriatrics* by Stevens-Neck and collaborators (2023), are challenging for patients, carers, and those devoted to developing new therapies for neurological disorders. Patients with rarer dementias have cognitive and behavioral changes that contrast with those of common dementias such as Alzheimer's disease, may respond differently to both pharmacologic and non-pharmacologic interventions, and pose unfamiliar challenges to all stakeholders. The rare dementias typically progress more rapidly than Alzheimer's disease and begin earlier in life. Death occurs more quickly and at a younger age than more common forms of dementia. It is this psychological aspect of preparing for the death of the patient with pre-death grief and loss that is the subject of the investigation and intervention by Stevens-Neck and colleagues (2023). In this perspective, I begin by reviewing challenges and strides in developing pharmacologic therapies for rarer dementias that can give hope to patients, carers, and clinicians; then I comment on the psychological impact of the rarer dementias and the observations reported in the paper by Stevens-Neck *et al.* (2023).

Rare diseases are common. This paradoxical statement is true because although each recognized condition is uncommon, the large number of rare causes of disease leads to a large population of affected individuals. There are an estimated 7000 (range from 4500 to 8000) rare diseases. "Rare" has several definitions globally and is defined in the United States as fewer than 200,000 individuals and in Europe as fewer than 1 in 2000 individuals (Haendel *et al.*, 2020). The rare disease population comprises between 350 and 475 million people globally (Adachi *et al.*, 2023). In the United States, the 7000 recognized rare diseases affect approximately 30 million individuals or nearly 10% of the population (fda.gov; rare diseases are Food and Drug Administration [FDA]). Fifty percent of those with rare diseases are children, signaling that half of the rare diseases have the onset in adulthood including mid and late life. Thirty to 50 percent of all rare diseases affect the nervous system with impact on cognition, function, and motor function.

There are 3.9 million individuals globally with early-onset dementia (Hendriks *et al.*, 2021). Onset in midlife or late midlife of these rapidly progressive disorders results in early compromise of the identity and then the life of the patient and produces enormous stress on carers. The societal toll is high as these brain disorders often occur when the affected individual is building a career, generating income, and raising a family.

There has been success in drug development for rare diseases. The Orphan Drug Act (Public Law 97-414 2013) provided incentives for rare disease drug development. In 2022, 20 new drugs were approved by the US FDA for the treatment of rare diseases, comprising 54% of all new drugs approved that year (Food and Drug Administration, 2023). Many of these drugs were for the treatment of rare forms of cancer; however, drugs for rare nervous system diseases were also approved including Relyvrio® (taurusodiol and sodium phenylbutyrate) for the treatment of amyotrophic lateral sclerosis and Amvuttra® (vutrisiran) to treat the peripheral neuropathy associated with hereditary transthyretin-mediated amyloidosis. Between 1983 when the orphan drug act became law and July 2020, 559 orphan products to treat rare diseases were approved and came to market. Prior to 1983, only 38 drugs to treat rare diseases existed. Most drugs

approved for rare diseases (75%) treat one rare disease and have no other indication for use. Seven percent of the drugs were originally approved to treat common diseases and were shown after approval to benefit a rare disease. Twenty-seven percent of the approved rare disease therapies are approved for the treatment of more than one rare disease. Despite these successes in rare disease drug development, 90% of rare diseases have no FDA-approved therapy (NORD, 2022).

Financial incentives put in place by the orphan drug legislation are important contributors to the success of orphan drug development for rare diseases. These incentives include tax credits, waiver of FDA user fees, extended periods of market exclusivity to increase the period of revenue generation from the approved drug, voucher programs, FDA grant programs, and small Business Innovation Research (SBIR) grants that can be devoted to rare disease drug development and clinical trials. FDA programs that can assist rare disease drug development include fast track designation, breakthrough disease designation, and accelerated approval (Yates and Hinkel, 2022). These incentives attract companies to devote their efforts to rare disease drug development with the expectation of higher success rates than in other non-incentivized, non-orphan indications. Support from patient advocacy groups has played an important role in orphan drug development for rare diseases. Advocacy can support companies involved in rare disease drug development, encourage patient participation, and facilitate empowering patients and families with a greater voice in the drug development process (Tsang *et al.*, 2019).

Seventy-five percent of rare diseases are caused by genetic mutations. This insight is of great importance for drug development. Identification of the mutation is one means of precise patient identification, the mutation may be subject to gene therapy, and restoration of the protein produced by the gene (in loss of function mutations) can serve as a biomarker of success of the intervention. The presence of a known mutation in a disorder can accelerate the development of transgenic animal models useful in early testing of therapeutic interventions (Murillo-Cuesta *et al.*, 2020). Gene therapy approaches, including viral vector mediated gene transfer, genome editing, and other nucleic acid therapeutics such as antisense oligonucleotides (ASO), are examples of genetic therapies for mutation-based rare diseases (Brooks *et al.*, 2016). Development programs with an established relationship between the genetic features of the disease and the candidate intervention have a higher success rate than development programs without this genetic foundation (Morgan *et al.*, 2018). Beyond genetics and genomics, other new technologies can be brought to bear on rare disease drug development including proteomics and other omic strategies, in silico drug design, quantitative systems pharmacology, organ-on-a-chip approaches, and induced pluripotent stem cell platforms for early-stage drug effect interrogation.

Clinical trials for rare diseases have many complexities and are challenging to conduct. There is often insufficient information on the natural history of the disorders to provide historical control information needed to predict the rate of decline in a placebo group with which to compare the effects of the test therapy; outcome measures have often not been optimized for rare disease populations since few individuals are available at any one site; most sites are unfamiliar with patients with the specific rare disorder included in the trial; insight into dosing is difficult to achieve when few patients are available to assess responses at different dose levels; and safety information will be limited given the small number of patients involved in the trials (Mellerio, 2022). Every individual with the disease of interest for the clinical trials is critically important, often resulting in including patients with a broad range of severities. Few outcome measures perform well across populations of patients with mild-to-severe disease. Biomarkers may be unavailable for some aspects of clinical trials such as measures of target engagement, disease monitoring, disease modification, or safety. Computational and bioinformatic approaches may assist in addressing some of these challenges; Bayesian type trials, for example, allow adjustments after trial initiation and guide the use of computational strategies to integrate information from disparate sources to increase study power (Carlin and Nollevaux, 2022). Regulatory flexibility in response to the challenges of orphan drug development is essential to successful outcomes and approval.

Although some types of dementia of late life are common, such as Alzheimer's disease and Parkinson's disease with dementia, most other forms of dementia are rare. These rare forms of dementias have no effective pharmacologic interventions making the contribution of Stevens-Neck and colleagues particularly relevant (2023). The dementias meeting criteria for rare diseases and orphan drug development include autosomal dominant Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis with dementia, frontotemporal dementia, progressive supranuclear palsy, corticobasal degeneration, and multiple system atrophy (Cummings, 2021).

Drug development programs are actively pursuing new therapies for rare dementia. Huntington's disease has been studied in trials of

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ASOs that are administered intrathecally and target interruption of production of the huntingtin protein implicated in the pathophysiology of the disease (Tabrizi *et al.*, 2019). Progranulin mutations are a rare cause of frontotemporal dementia, and several development programs are advancing trials of drugs aimed at increasing progranulin levels (Panza *et al.*, 2020). Mutation carriers have low levels of plasma progranulin that can serve as a biomarker for patient identification and possibly for monitoring therapeutic response (Finch *et al.*, 2009). Progressive supranuclear palsy and corticobasal degeneration are tauopathies and have been the focus of trials of anti-tau therapies (Hoglinger *et al.*, 2021). There are no approved therapies for any of these disorders, but the promising targets and emerging candidate therapies indicate that new treatments to prevent or delay the onset or slow the progression can be anticipated. Recent successes in the development of disease-modifying agents for Alzheimer's disease provide insights into drug development for neurodegenerative diseases that can be applied to rare disease programs (Mintun *et al.*, 2021; van Dyck *et al.*, 2022).

The absence of pharmacotherapies for rare dementias increases the importance of psychosocial interventions including interventions for both patients and carers. Even with successful trials and approved drugs most patients will not be cured of their illnesses, and the psychosocial interventions will continue to play critically important roles in the lives of patients and families. Stevens-Neck and colleagues identify the pre-death grief that commonly occurs and is uncommonly recognized or addressed as carers anticipate the expected death of their loved one. In a vanguard study of a small group of carers, they created an online pre-death grief education and discussion support group called the Road Less Travelled. The program consisted of six 2-hour sessions held every other week. Two facilitators, including an experienced dementia care nurse, led the discussions. Carers of rarer dementia patients self-identified in response to an email and were screened by program staff for appropriateness. Quantitative scale scores were collected, and unstructured discussions were conducted to understand the experience of the carers in the program. Using an online meeting platform, the session explored grief, adapting to loss, normalizing the grief experience, and embracing the end of life. The program participants had a very positive response to the program. Many found the opportunity to reflect on their situations and their feelings particularly valuable. Participants reported experiencing less anger, frustration, guilt, and burden in response to the discussions. Scale scores demonstrated reduced depression and improved quality of life. Will this program generalize, and can it be scaled to meet the needs of the many who could be helped? These questions will be answered going forward. The preliminary results are sufficiently promising that further study of the program and consideration of widespread implementation are warranted.

Conflicts of interest

JC has provided consultation to Acadia, Actinogen, Acumen, AlphaCognition, Aprinoia, AriBio, Artery, Biogen, BioVie, Bristol-Myers Squib, Cassava, Cerecin, Diadem, EIP Pharma, Eisai, GemVax, Genentech, GAP Innovations, Janssen, Jocasta, Karuna, Lighthouse, Lilly, Lundbeck, LSP/EQT, Merck, NervGen, Novo Nordisk, Oligomerix, Optoceutics, Ono, Otsuka, PRODEO, Prothena, ReMYND, Roche, Sage Therapeutics, Signant Health, Simcere, Suven, SynapseBio, TrueBinding, Vaxxinity, and Wren pharmaceutical, assessment, and investment companies.

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