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THE HEALTH PROMOTION MODEL AND RARE DISEASE PATIENTS: A MIXED METHODS STUDY EXAMINING ADHERENCE TO TREATMENT IN MEN WITH CONGENITAL HYPOGONADOTROPIC HYPOGONADISM

Dwyer Andrew A.

UNIL | Université de Lausanne
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Prof. Nelly Pitteloud, UNIL, Codirectrice de thèse
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Experts	Monsieur	Prof. José **Côté**
	Monsieur	Dr Patrick **Bodenmann**

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Monsieur Andrew Dwyer

Master of Science in Nursing, Massachusetts General Hospital Institute of Health Professions Boston, USA

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Lausanne, le 10 novembre 2014

pour La Doyenne
de la Faculté de Biologie et de Médecine

Directrice de l'IUFRS

Directrice de l'Ecole Doctorale

Abstract

Rare diseases are typically chronic medical conditions of genetic etiology characterized by low prevalence and high complexity. Patients living with rare diseases face numerous physical, psychosocial and economic challenges that place them in the realm of health disparities. Congenital hypogonadotropic hypogonadism (CHH) is a rare endocrine disorder characterized by absent puberty and infertility. Little is known about the psychosocial impact of CHH on patients or their adherence to available treatments.

This project aimed to examine the relationship between illness perceptions, depressive symptoms and adherence to treatment in men with CHH using the nursing-sensitive Health Promotion Model (HPM). A community based participatory research (CBPR) framework was employed as a model for empowering patients and overcoming health inequities. The study design used a sequential, explanatory mixed-methods approach. To reach dispersed CHH men, we used web-based recruitment and data collection (online survey). Subsequently, three patient focus groups were conducted to provide explanatory insights into the online survey (i.e. barriers to adherence, challenges of CHH, and coping/support)

The online survey (n=101) revealed that CHH men struggle with adherence and often have long gaps in care (40% >1 year). They experience negative psychosocial consequences because of CHH and exhibit significantly increased rates of depression ($p<0.001$). Focus group participants (n=26) identified healthcare system, interpersonal, and personal factors as barriers to adherence. Further, CHH impacts quality of life and impedes psychosexual development in these men. The CHH men are active internet users who rely on the web for

crowdsourcing solutions and peer-to-peer support. Moreover, they are receptive to web-based interventions to address unmet health needs.

This thesis contributes to nursing knowledge in several ways. First, it demonstrates the utility of the HPM as a valuable theoretical construct for understanding medication adherence and for assessing rare disease patients. Second, these data identify a range of unmet health needs that are targets for patient-centered interventions. Third, leveraging technology (high-tech) effectively extended the reach of nursing care while the CBPR approach and focus groups (high-touch) served as concurrent nursing interventions facilitating patient empowerment in overcoming health disparities. Last, these findings hold promise for developing e-health interventions to bridge identified shortfalls in care and activating patients for enhanced self-care and wellness.

Abrégé

Les maladies rares sont généralement de maladies chroniques d'étiologie génétique caractérisées par une faible prévalence et une haute complexité de traitement. Les patients atteints de maladies rares sont confrontés à de nombreux défis physiques, psychosociaux et économiques qui les placent dans une posture de disparité et d'inégalités en santé. L'hypogonadisme hypogonadotrope congénital (CHH) est un trouble endocrinien rare caractérisé par l'absence de puberté et l'infertilité. On sait peu de choses sur l'impact psychosocial du CHH sur les patients ou leur adhésion aux traitements disponibles.

Ce projet vise à examiner la relation entre la perception de la maladie, les symptômes dépressifs et l'observance du traitement chez les hommes souffrant de CHH. Cette étude est modélisée à l'aide du modèle de la Promotion de la santé de Pender (HPM). Le cadre de l'approche communautaire de recherche participative (CBPR) a aussi été utilisé. La conception de l'étude a reposé sur une approche mixte séquentielle. Pour atteindre les hommes souffrant de CHH, un recrutement et une collecte de données ont été organisées électroniquement. Par la suite, trois groupes de discussion ont été menées avec des patients experts impliqués au sein d'organisations reliés aux maladies rares. Ils ont été invités à discuter certains éléments additionnels dont, les obstacles à l'adhésion au traitement, les défis généraux de vivre avec un CHH, et l'adaptation à la maladie en tenant compte du soutien disponible.

Le sondage en ligne (n = 101) a révélé que les hommes souffrant de CHH ont souvent de longues périodes en rupture de soins (40% > 1 an). Ils vivent des conséquences psychosociales négatives en raison du CHH et présentent une augmentation significative des taux de dépression ($p < 0,001$). Les participants aux groupes de discussion (n = 26) identifient

dans l’ordre, les systèmes de soins de santé, les relations interpersonnelles, et des facteurs personnels comme des obstacles à l'adhésion. En outre, selon les participants, le CHH impacte négativement sur leur qualité de vie générale et entrave leur développement psychosexuel. Les hommes souffrant de CHH se considèrent être des utilisateurs actifs d'internet et comptent sur le web pour trouver des solutions pour trouver des ressources et y recherchent le soutien de leurs pairs (peer-to- peer support). En outre, ils se disent réceptifs à des interventions qui sont basées sur le web pour répondre aux besoins de santé non satisfaits.

Cette thèse contribue à la connaissance des soins infirmiers de plusieurs façons. Tout d'abord, elle démontre l'utilité de la HPM comme une construction théorique utile pour comprendre l'adhésion aux traitements et pour l'évaluation des éléments de promotion de santé qui concernent les patients atteints de maladies rares. Deuxièmement, ces données identifient une gamme de besoins de santé non satisfaits qui sont des cibles pour des interventions infirmières centrées sur le patient. Troisièmement, méthodologiquement parlant, cette étude démontre que les méthodes mixtes sont appropriées aux études en soins infirmiers car elles allient les nouvelles technologies qui peuvent effectivement étendre la portée des soins infirmiers (« high–tech »), et l'approche CBPR par des groupes de discussion (« high-touch ») qui ont facilité la compréhension des difficultés que doivent surmonter les hommes souffrant de CHH pour diminuer les disparités en santé et augmenter leur responsabilisation dans la gestion de la maladie rare. Enfin, ces résultats sont prometteurs pour développer des interventions e-santé susceptibles de combler les lacunes dans les soins et l'autonomisation de patients pour une meilleure emprise sur les auto- soins et le bien-être.

Dedication

I dedicate this thesis to all the patients with

congenital hypogonadotropic hypogonadism who

are struggling to overcome feelings of shame and isolation.

Preface

This doctoral thesis is a thesis by article. As detailed in the table of contents, the first chapters are constructed in a traditional manner: Part I - Introduction, Part II - Literature Review and presentation of the theoretical model, Part III - Methods. Subsequently, the results (Part IV) are presented as a sequence of three manuscripts that have been submitted to peer-review journals followed by a summary of the overall project (Part V). As requested by the Doctoral program, one of these article (Article 1) has been already accepted for publication. The two other articles (article 2 and 3) have been submitted and are currently under review.

Manuscripts submitted for peer-review:

1. Dwyer, R. Quinton, D. Morin & N. Pitteloud (2014) Identifying the unmet health needs of patients with congenital hypogonadotropic hypogonadism using a web-based needs assessment: Implications for online interventions and peer-to-peer support". *Orphanet Journal of Rare Diseases.* Article accepted (June 4, 2014 – Appendix 10). Published June 11, 2014. (doi: 10.1186/1750-1172-9-83, PMID:24915927)

2. A. Dwyer, J. Tiemensma, R. Quinton, N. Pitteloud & D. Morin (2014) Affected illness representations, depressive symptoms and adherence to treatment in men with congenital hypogonadotropic hypogonadism. *Journal of Clinical Endocrinology and metabolism.* Article submitted (Submitted April 12, 2014 - Confirmation of submission Appendix 11)

3. A. Dwyer, R. Quinton, N. Pitteloud, D. Morin (2014) Psychosexual development in men with congential hypogonadotropic hypogonadism on long-term treatment: A mixed-methods study. *Journal of Sexual Medicine.* (April 14, 2014 - Confirmation of submission Appendix 12)

Contributions of authors are as follows:

- Conception and design: Andrew Dwyer, Nelly Pitteloud, Diane Morin.
- Acquisition, analysis and interpretation of data: Andrew Dwyer.
- Drafting the articles: Andrew Dwyer.
- Review of data interpretation and comments on intellectual content: Richard Quinton, Jitske Tiemensma, Nelly Pitteloud, Diane Morin.
- Revisions and final manuscripts preparation: Andrew Dwyer.
- Final approval of the completed manuscripts: Andrew Dwyer, Richard Quinton, Jitske Tiemensma, Nelly Pitteloud, Diane Morin.

List of Figures and Tables

Abreviations and Acronyms

Congenital hypogonadotropic hypogonadism	CHH
European Cooperation in Science and Technology	COST
Common Sense Model	CSM
European Organization of Rare Diseases	EURORDIS
European Union Committee of Experts on Rare Diseases	EUCERD
European Union	EU
Follicle stimulating hormone	FSH
Food and Drug Administration	FDA
Gonadotropin-releasing hormone	GnRH
Health Belief Model	HBM
Health Promotion Model	HPM
Human chorionic gonadotropin	hCG
Hypothalamic-pituitary-gonadal	HPG
Institute of Medicine	IOM
International Classification of Diseases	ICD
Illness Perception Questionnaire Revised	IPQ-R
Kallmann syndrome	KS
Luteinizing hormone	LH
Morisky Medication Adherence Scale	MMAS
National Institutes of Health	NIH
National Organization for Rare Disorders	NORD
Testosterone replacement therapy	TRT
Testosterone	T
United States	US
World Health Organization	WHO
Zung Self-rating Depression Scale	SDS

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As for my collaborators, I thank Dr. Jitske Tiemensma for her willingness to conduct an online collaboration as well as for sharing data and insights on illness perceptions - I hope that we will be able to meet face-to-face one day soon. I am indebted to colleague and friend Dr. Richard Quinton for his lengthy and insightful discussions as well as for hosting me during the COST Short-Term Scientific Mission. I thank Mr. Neil Smith and the other patient community leaders not just for their tireless patient advocacy, but also for their collaboration and friendship. I also wish to acknowledge my colleague Dr. Gerry Sykiotis for his helpful manuscript critiques and Ms. Virginia Hughes for her encouragement in including patient perspectives in the process. Further, I am grateful for the funding support form the Endocrine Nurses Society and COST Action BM1105.

I would be remiss if I did not express my gratitude to several key individuals in my career - Martha Heck, Prof. Cheryl Cahill, and Dr. Edward T. Heck. Martha lit the lamp on my

nursing career, Cheryl was my first nursing research mentor and Ed's "10,000 repetitions" continue to help me navigate my career path. I thank my parents for their support and in particular my Mother for asking the right questions and giving the right words of encouragement during this process. I am grateful for the patience of my daughters Julia and Mia who have put up with me working late, writing during the weekends and being away from home. Most importantly, I thank my loving wife and partner Krista Chavez. There are not enough pages to explain how many different ways she has made this thesis possible. She has listened, encouraged, and believed in me from the outset and has been an amazing single parent in my absence. Krista has continued to push me to be the best human being that I can be and to never forget that one person can (and often does) make all the difference in the world.

Table of Contents:

Chapter I: Introduction

What is a Rare Disease?

Rare diseases are disorders that affect a small number of individuals. These so-called "orphan diseases" are often related to genetic determinants and can be life threatening or may result in chronically debilitating disease. These rare conditions pose challenges for patients as well as for the healthcare providers who care for them.

There is no universally accepted definition of what makes a disease rare. In the European Union (EU), rare is considered as affecting no more than 1 in 2,000 individuals while the incidence is set at 1 in 1,250 in the United States (US) (van Weely & Leufkens, 2004). Remarkably, the World Health Organization (WHO) estimates that there are approximately 5,000-8,000 rare diseases and the vast majority are much rarer than either EU or US definitions (Remuzzi & Garattini, 2008). Individually these conditions are infrequent, yet the cumulative effect is quite large as there are an estimated 30 million European rare disease patients, a figure roughly the same as the combined populations of the Netherlands, Belgium and Luxembourg (van Weely & Leufkens, 2004).

Despite the differences in how governing bodies have defined rare, beyond low prevalence there is a general agreement of common themes related to these rare conditions including significant morbidity/mortality, inadequate treatment(s), and insufficient research on these disorders. In 1983, the US Congress passed the "Orphan Drug Act" which defined a rare disease as disease with a prevalence of <200,000 persons (Asbury, 1991). By this definition, there are more than 7,000 rare disorders, affecting, an estimated 25 million persons in the US (approximately 10% of the population) (Griggs et al., 2009). This legislation resulted from the recognition of the unique challenges faced by patients and families affected by rare diseases; a

lot of which are genetic, poorly understood, life-threatening or chronically debilitating, and without cure or effective treatment. Because of these combined factors and the low prevalence of these diseases, special combined efforts are required for nursing and health care in general to address them.

Impact of Living with a Rare Disease:

The WHO (2006) defines health as "*a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*" and declares that "*the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without the distinction of race, religion, political belief, economic or social condition*" (page 1) . This reminds us that beyond the statistical criteria defining a disease as rare, there is the patient who lives with the disease, and to whom it is a central part of life. Even for those rare conditions that may be less severe and not life-threatening, the sense of isolation, uncertainty about how the disease will progress, and the lack of effective treatment can have a significant impact on attaining the best possible standard of health (Cohen & Biesecker, 2010; Institute of Medicine (IOM), 2010; van der Kloot et al., 2010) Accordingly, the impact of having a rare condition extends beyond the disease-specific effect on physical health and includes affects on psychosocial wellbeing and the socioeconomic implications of having a rare disorder (Wastfelt, Fadeel, & Henter, 2006). The general consensus shared by patients and health authorities alike is that patients affected by rare diseases are faced with similar challenges including: (1) lack of scientific knowledge of their disease, (2) lack of access to correct diagnosis, (3) delays in diagnosis, (4) lack of appropriate multidisciplinary healthcare, (5) lack of quality information and support at the time of diagnosis, (6) negative social consequences, (7) inequities and difficulties in access to treatment, rehabilitation and care, (8) dissatisfaction with and loss of confidence in medical and social services and, (9) rejection by health professionals (EURORDIS, 2009).

The European Organization of Rare Diseases (EURORDIS) utilized existing patient organizations to conduct extensive surveys (EurordisCare2 and EurordisCare3) examining the experiences of patients with 16 rare diseases across 22 European nations. The results were published in a report entitled "The Voice of 12,000 Patients" and revealed a number of poignant observations such as the following. In order to arrive at an accurate diagnosis, 18% of patients reported often having to seek out answers on their own, with little help from the health-care system and 25% stated they had to wait more than 3 years for the correct diagnosis. Notably, 41% of patients were initially misdiagnosed, 7% of whom were told that their condition was psychosomatic. Further, when a proper diagnosis was identified, 35% of patients felt the method of communicating the diagnosis was unsatisfactory (i.e. having information given in hospital corridors, by telephone, or in writing alone). Overall, these experiences led to an erosion of confidence in the healthcare system as reported by 19% of survey participants. Additionally, nearly 1 in 5 patients (18%) stated having experienced rejection by a healthcare professional because of the complexity of the rare disease or its associated symptoms (EURORDIS, 2009).

The EURORDIS report supports the notion that there is insufficient access to information and medical or nursing expertise in relation to rare diseases. Patients and families struggle to get appropriate healthcare with 26% reporting difficulty or inability to access care and services including lack of appropriate referral. Further, rare diseases and chronic and care often requires a multidisciplinary approach involving different medical services which patients report as often being poorly coordinated (EURORDIS, 2009). Disenfranchised by the rare nature of their diseases and the frustration with the healthcare system, many patients and

families express a desire to connect with others with a rare disease, either the same of a different condition (Huyard, 2009).

Technology Connects Patients with Rare Diseases:

For patients with rare diseases, finding disease specific information and creating community with others like themselves is daunting given the dispersed nature of specialized referral centers and affected individuals/families. However, over the past 30 years, advances in telecommunications have dramatically changed the way people seek and consume information (Lober & Flowers, 2011). The first personal computers were introduced in the early 1980s and the 1990s witnessed the dawning of the internet. Many users were drawn to the internet following the introduction of electronic mail (e-mail) in the early 1990s and virtual communities grew as online access became faster and more widely available. Indeed, internet hosts grew in number from approximately 9 million in 1995, to over 100 million by the late 2000s (Lober & Flowers, 2011). The increased internet access and more widely available hot-spots for wireless connection paralleled the development of mobile devices and the increased use of laptop computers, internet capable cellular phones, and small tablet devices (Figure 1).

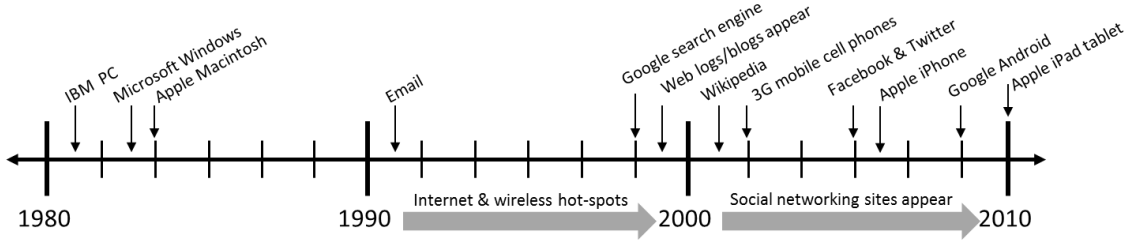

Figure 1. Advances in information and telecommunications technology.

Introduction of significant products and services are depicted by arrows above the timeline. The gray arrows below the timeline denote trends including introduction of the internet the

increasing availability to internet access/wireless hot-spots and the emergence of internet enabled social networking.

This evolving technology has both increased access to information and has facilitated new modes of communication. For rare disease patients, the ability to connect over vast distances has created a perceptual shift. The New York Times columnist Thomas L. Freidman, wrote about the change brought about in part by the internet referring to it as a "flattening of the world" (Freidman, 2005) wherein people have access to unprecedented amounts of information and potential for connectivity around the globe. This new media allows dispersed people to create virtual communities via social networks, bringing together people who would otherwise never meet face-to-face enabling interactivity and "crowdsourcing", or taking advantage of the combined knowledge, talents, and problem solving abilities of a group (Howe, 2006). These so-called communities of knowledge, communities of practice or communities of sharing have simultaneously spread in the health care and nursing sectors.

These technologic advances have been embraced by the rare disease community as evidenced by the 2011 Pew Report on the use of internet in peer-to-peer healthcare (Fox, 2011). In a survey of over 3,000 adults living in the US, the Pew Report demonstrated that one in almost five (18%) of internet users have gone online to find others who share similar health concerns. Further, while most people taking part in this survey turn to a healthcare professional such as a doctor or nurse for technical information, non-professionals and peers were favored for emotional support in dealing with a health issue and for seeking answers related to everyday health issues. Professionals and non-professionals were considered equally important for advice in coping with day-to-day health situations. A second part of this study included an internet survey of more than 2,000 individuals affected by a rare disease. The study identified individuals with chronic conditions or rare diseases as the most likely to augment professional

medical advice with online peer-to-peer connections. Further, patients and caregivers of those living with a rare disease reported drawing upon their peer network during their time of need even more so than those with a more common chronic health condition (Fox, 2011).

Rare Diseases: Getting Organized

As depicted in "The Voice of 12,000 Patients", patients and families affected by rare diseases face challenges in finding accurate information about their condition and in accessing appropriate care (EURORDIS, 2009). Within the crucible of rare diseases, patients and families have begun to utilize technology and social media to expand their support network and cope with the unique challenges they face in dealing with exceedingly uncommon medical conditions. When the Orphan Drug Act was passed in 1983, there were relatively few rare disease patient organizations. However, working collectively, they provided crucial advocacy which promoted the passage of the landmark legislation. Shortly thereafter, the National Organization for Rare Disorders (NORD) was formed (Putkowski, 2010). It was one of the first organizations to promote awareness of rare diseases and providing public policy advocacy, patient friendly information and assistance programs.

In 1986, the Genetic Alliance was established to focus attention on groups promoting advocacy for genetic conditions. In 1997, the EURORDIS created an alliance of patient associations committed to improving the quality of life of all those living with rare diseases. EURORDIS has been a leader in advocating for the European Regulation of Orphan Drugs (Parliament, 1999) and the forming of the European Union Committee of Experts on Rare Diseases (EUCERD) which develops and monitors programs to provide quality care for patients with rare diseases. Projects include developing European reference networks for rare diseases, promoting cross border healthcare to improve access to quality care for rare disease patients, improving the visibility and promoting awareness of rare diseases via the Orphanet

database, improving coding and classification of rare diseases including revisions to the International Classification of Diseases (ICD), improving better access to orphan drugs, and pooling European expertise on rare diseases, and developing metrics and health indicators for rare diseases (Holmes, 2012).

Such groups have been critical in making rare diseases a growing priority for healthcare providers, public health authorities, and policy makers alike (Figure 2).

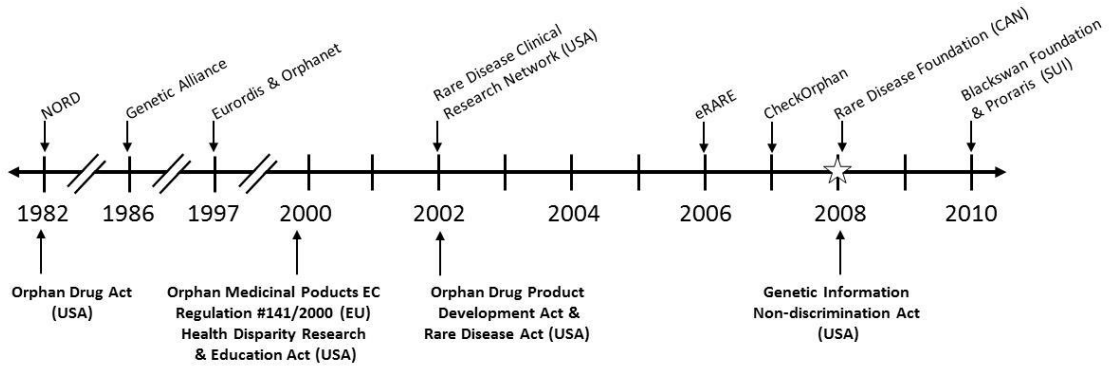

Figure 2. Timeline of legislation and organizations related to rare diseases. The establishment of organizations and key programs related to rare diseases are depicted by arrows above the timeline. Seminal legislative acts related to rare diseases are noted by arrows below the timeline. The star depicts the first International Rare Disease Day.

Inequalities for People Living with Rare Diseases

Though rare diseases are numerous in total, the rarity of the individual conditions can result in patients and families feeling marginalized and the psychosocial impact of perceived invisibility, isolation, and feelings of powerlessness can have tremendous deleterious impact on quality of life (Cohen & Biesecker, 2010; Huyard 2009; Nettleton, Watt, O'Malley, & Duffy, 2005). While the adoption of several legislative acts have benefitted patients and

families affected by rare diseases (Figure 2), a confluence of conditions create disparity in access to quality care and in allocation of social support of rare diseases.

Firstly, people with rare diseases have difficulty in finding diagnostic expertise causing delays in diagnosis and receiving quality care (Schieppati, Henter, Daina, & Aperia, 2008). Secondly, most rare diseases are genetic and have no identified cure creating an unusually high stress and burden on family and children at risk to inheriting the condition (Aubeeluck & Moskowitz, 2008). Thirdly, a universally acknowledged coding system is lacking to properly identify patients, enable international registries, thus preventing accurate assessment of the economic and social consequences associated with rare diseases. The development of novel therapies is inhibited by a lack of profit potential and payback for investment in drug development (Scheindlin, 2006), researchers and clinicians face both funding and training challenges in pursuing careers related to rare diseases (Griggs et al., 2009; Hampton, 2006), and attempts to establish best practices or evidence based strategies are hindered by small samples sizes and recruitment problems related to dispersed population (Kruer & Steiner, 2008; Watson et al., 2008). Further, patients with rare diseases also face economic challenges related to chronic care needs as they often require frequent medical care related to long-term health problems, available treatments are often prohibitively expensive and there is significant concern regarding discrimination related to employment and health insurance (Bombard et al., 2008; Penziner et al., 2008). As such, the physical, psychosocial and economic impact of living with a rare disease is to be viewed as a social determinant of health disparity (Holtzclaw Williams, 2011). Because of these inequalities, these patients can be characterized as underserved and vulnerable populations. However, little is known about what kind of approaches to care or nursing services these patients find most important and wish for.

Challenges to Health and Empowerment in Rare Diseases

Patients affected by rare diseases are a community that faces numerous challenges to wellbeing. If we accept the WHO delineation of health as an inalienable human right, then by logical extension, we must also strive to remove disparities and seek to attain equality and health for all people (Starfield, 2007). Marginalized and disenfranchised communities often lack the power to take action to remove barriers in their lives. Accordingly, powerlessness is an acknowledged negative determinant of health (Wallerstein, 1992). To remove barriers and facilitate health requires empowerment, i.e. the process by which people individually or/and collectively gain control over the factors and transform decisions creating desired outcomes that shape their lives (WHO, 2009). Empowerment has been acknowledged as a critical component of shared decision making process, patient-centered care, and achievement of better health outcomes (Maizes, 2009; Stewart et al., 2000). Given the unique challenges faced by patients with rare diseases, from a nursing perspective, empowerment becomes a central issue for this community of patients (Ayme, Kole, & Groft, 2008).

The Social Cost of Rare Diseases

The past 30 years has witnessed the growing voice of patients in many disease-related experiences and the emergence of the patients' movement which has led to the growing recognition that specifically, rare diseases are not only a medical issue, but an important social issue as well. The patients' movement emerged from the recognition that patients are a distinct group of individuals facing similar obstacles who share common experiences. Further, the patients' movement is based on the notion that patients have a knowledge base that is both distinct and separate from health professionals, and that patients are entitled to a legitimate say in making the decisions around their condition (Ayme et al., 2008). Activated patients have played important roles in drawing attention to rare disease issues and the legislation and increased government funding of rare disease initiatives emerged from the combined activities

of patient advocacy groups, academia (including the basic science and translational research investigators from universities and academic medical centers), and politicians (Figure 2). Indeed, the EURORDIS, Orphanet, and the European Commission projects (Orphanet, 2005) have helped raise awareness of the social justice issues related to rare diseases (Schieppati et al., 2008). As part of the patients' movement, patients and families have embraced technology and emerging social media as a way to combat the marginalizing effects of being diagnosed with a rare disease by drawing on each other for both emotional support, experiences, and information (Denecke, 2009). This support system has helped patients and families affected by rare diseases become more engaged with the healthcare system and to take a more active role in the health-related decision making process (Ayme et al., 2008).

This activism has addressed the lack of effective treatment for many rare diseases. Advocacy groups have spurred calls for international collaboration between governments and industry stakeholders to accelerate the pace of translational research discoveries by engaging patients and establishing patient registries to facilitate recruitment into clinical trials and help speed the process of brining novel therapies to market (Griggs et al., 2009; Kruer & Steiner, 2008; Watson et al., 2008). Additionally, political action has identified rare diseases as a growing priority (Figure 2) and legislation enacted in the US and EU to remove some of the financial disincentives related to rare disease drug development has helped entice investment from the pharmaceutical industry to develop rational new therapies and facilitate collaboration of a higher order. The landmark Orphan drug act (1984) also designated conditions as "rare" in the event that there is little expectation to recoup costs for developing and bringing to market a drug for a condition with limited number of effected individual. Since approval, more than 110 pharmaceutical companies in the U.S. have received marketing approval from the Food & Drug Administration (FDA) for an orphan product and a number biotechnology companies,

such as Genentech, Amgen, and Genzyme, had an orphan drug as their first product to receive market approval (Haffner, Whitley, & Moses, 2002). Legislation has changed the pace at which orphan drugs are brought to market. In the 10 years prior to the passing of the 1983 Orphan Drug Act, only 10 treatments for rare diseases received FDA approval in contrast to the 280 receiving approval in the 14 years following the adoption of this legislation (Haffner, 2006). Attention to rare diseases has changed over the past decades, yet with an estimated 250 new rare diseases being identified each year (Wastfelt et al., 2006), much work remains to be done.

In summary, patients affected by rare diseases represent a broad and diverse group of individuals and each rare condition has its own and unique set of health and social challenges. Accordingly, it is poignant to consider that in order to strive for a level of health (and healthcare) to which all should be entitled, these patients had little choice but to become amongst the most active and empowered members of the broader health community (EURORDIS, 2009). Patients, families, and advocacy groups have made tremendous strides in raising the awareness about rare diseases, and they have been joined by clinicians, academics, members of industry, and politicians alike in beginning to address the inequalities and health disparities faced by this community. Each of these groups has recognized on some level that patients affected by rare diseases do not exist in isolation, rather, rare diseases impact families, communities, the health care system, and the health care financing. The healthcare professionals such as nurses who care for these patients are often reminded of the gap between patient needs and our inability to address and meet these needs. Thus, the background reviewed to this point suggests that patients with rare diseases are faced with many unique challenges and that the approaches applied to date have been insufficient in addressing the needs of these patients.

The Role of Nursing in Rare Diseases Using a Health Promotion Perspective

In a very broad sense, nursing involves working with individuals, families, and communities to create optimal conditions for the highest attainable level of health and well-being. Nursing interventions address physical, emotional, and spiritual needs of patients to promote goal-directed actions, self-care, and satisfying relationships with others in striving for the highest attainable level of health. Nursing promotes coping, self-care, and adaption in meeting physiologic and relational needs, while maintaining emotional/spiritual integrity and supporting a positive self concept and an intact identity (Pender, Murdaugh, & Parsons, 2010). This definition is regardless of current health status.

Also, nursing and social justice are connected through a lengthy history dating back to Florence Nightingale, who is credited as the founder of modern professional nursing (Manthey, 2008). Nightingale's approach to nursing is explicated in 1855 in her book "Notes on Nursing: What it is and what it is not" from which emerge the humanistic tenets of nursing including respect, care, and empowerment (Nightingale, 1992). Indeed, Nightingale recognized existing power structures, in her case between the nurse/carer and the patient, and comments on the importance of not talking "to" or "at" patients, but rather speaking "with" them. This goal oriented advice, aimed at deconstructing power-based barriers, mirror the writings of Paolo Freire, who described the concept of powerlessness over a hundred years later (Freire, 1970). Freire used this term to describe when the individual assumes a passive role as an object, rather than an active subject, acting on the environment (Freire, 1970). Nightingale's writings on respect for patients and nursing actions aimed at eliminating barriers provide a historical link between empowerment and nursing.

Importantly, an element that separates nursing from other health professionals is that nursing is not solely focused on ameliorating the illness but also is focused on the patient's reaction to illness. The holistic, patient-centered approach of nursing provided in the context of the Health Promotion Model can therefore be utilized to: i) identify the unmet bio-psycho-social-spiritual needs of patients with rare diseases, ii) identify the perceived barriers to health, and iii) develop targeted interventions and empowering patients to adopt health promoting behaviors. This holistic view has relevance for patients with rare diseases as it places the definition of health in the context of the individual - including those faced with severe disability or facing a life threatening illness.

In summary, nursing's role in addressing the needs of patients and families affected by rare diseases is relevant because the humanistic approach that nursing brings is at once empowering, and can be transformative by its very nature. It is so for rare diseases which are often genetic conditions that are poorly understood and often are without cure or effective treatment and have significant impact on patients and families. These are considered as chronic conditions that require care throughout life and nursing has played in important role in chronic disease management (Bodenheimer, MacGregor, & Stothart, 2005). Further, as nursing interventions have been effective in addressing health disparities as well as closing the gaps, cracks and shortfalls in the continuity of care for patients with chronic conditions, it would follow that nursing can make important contributions that will positively impact patients and families affected by rare diseases. Herein, the nursing's Health Promotion Model has been considered the most useful for understanding and addressing the unmet needs of patients with rare diseases (Pender, Murdaugh, & Parsons, 2010).

Research General Objective

Given these elements, this research project aims to examine the unmet health needs of patients with the specific rare condition of congential gonadotrpin-releasing hormone (GnRH) deficiency (resulting in congenital hypogonadotropic hypogonadism, CHH) using the nursing framework of Pender's Health Promotion Model (Pender, Murdaugh, & Parsons, 2010). This nursing-based needs assessment study is the needed step to develop a program of innovative nursing interventions to enhance health promoting behaviors and to develop patient-focused approaches to care in order to improve nursing sensitive and health-related outcomes.

Chapter II: Literature Review

The focus of this literature review is threefold: i) to provide an extensive presentation of the rare disease, congenital GnRH deficiency (CHH) presenting the clinical portrait and the pathophysiological characteristics of the disease as well as describing its impact on patients and families; ii) to describe the types of care programs that have been developed for such patients and carefully scrutinize the nursing components of these programs, as well as their expected or measured outcomes; and iii) to evaluate the framework of Pender's Health Promotion Model in relation to roles nursing plays in empowering patients via education, advocacy, enhancing coping, developing self-care skills, and building self-efficacy.

Therefore, the first search strategy used the keywords (synonymous terms) related to the condition such as "congenital GnRH deficiency", "Kallmann syndrome", "idiopathic hypogonadotropic hypogonadism", and "isolated GnRH deficiency" upon which additional search terms "genetics", "phenotype", and "treatment" were mapped in order to identify relevant publications related to congenital GnRH deficiency. This NCBI PubMed search was narrowed using the filters past 10 years, humans, and English language yielding a total of 331 publications (Appendix 1). After careful review, 65 citations were included in the literature review of congenital GnRH deficiency because of their high relevance, impact, and timeliness. Additionally, references of the selected articles were reviewed and historically important and seminal publications in the field were also included.

The second search strategy investigated the types of care programs and nursing interventions used in this patient population. Searches of the NCBI PubMed, CINAHL, and PsychINFO databases were used to retrieving the best possible up-to-date evidence from the past 10 years (2002-2012). Multiple MeSH and free-word searches were performed combining disease

synonyms (i.e. “congenital GnRH deficiency”, “Kallmann syndrome”, “idiopathic hypogoandotropic hypogonadism”, and “isolated GnRH deficiency”) that were focused using Boolean syntaxes combined with the MeSH and free-word terms “nursing”, “intervention”, “needs assessment”, “patient centered”, “self care”, “adherence”, “medication”, “patient compliance”, “attitude to health” (Appendix 2). This wide search failed to yield any relevant publications. Accordingly the search was expanded by broadening the disease term to include “hypogonadotropic hypogonadism” a less specific MeSH term encompassing the condition yielding 282 citations. The vast majority of which related to age-related hypogonadism, however after careful scrutiny, 5 citations (including studies of patients with Klinefelter syndrome, and review articles on androgen therapy) were deemed relevant and were included. As congenital GnRH deficiency is a rare, genetic, reproductive endocrine disorder “rare disease” was also explored to seek additional relevant citations (n= 297) and after careful review identified 18 relevant citations. Lastly, additional relevant citations were sought using the MesH term “endocrine system diseases” that identified nearly 2,000 citations and as such additional filtering was needed to obtain a more reasonable list of potentially relevant citations (Appendix 2). In the final analysis 30 of these were included.

In summary, no relevant care programs were identified specifically for congenital GnRH deficiency, and the articles retrieved for rare diseases primarily related to three central themes: empowerment, disparities, and multidisciplinary teams for care. In contrast to the very rare endocrine disorder of congenital GnRH deficiency, diabetes mellitus is a relatively common endocrine disorder yet both require chronic care. Due to the growing incidence and significant morbidity associated with type 2 diabetes a great deal of attention has been focused on this area. Therefore, I examined chronic care programs targeted at improving chronic care for diabetes to explore nursing’s role on providing comprehensive

interdisciplinary care and to identify successful models that could be applicable to patients with rare, chronic diseases. Lastly, a review of the literature identified 21 relevant citations form the past 10 years relating to Pender's Health Promotion model. References cited in these publications were reviewed to include additional relevant citations as well as Pender's most recent textbook explicating the HPM.

Clinical Portrait of Congenital GnRH Deficiency

Congenital GnRH deficiency is a genetic disorder which is clinically characterized by incomplete/absent puberty and infertility. Because it is a rare condition, incidence is difficult to assess (Seminara, Hayes, & Crowley, 1998) with published estimates range from 1 in 4,000 to 10,000 in a study of French conscripts (Fromantin, Gineste, Didier, & Rouvier, 1973), to 1/86,000 in a Sardinian military study (Filippi, 1986). Additionally, it is 2-5 times more frequent in males than females (Hu, Tanriverdi, MacColl, & Bouloux, 2003; Quinton et al., 2001; Seminara et al., 1998). Most cases are sporadic, keeping with a condition which impairs fertility, yet approximately a third of cases display a familial pattern of inheritance (Quinton et al., 2001; Seminara et al., 1998). Congenital GnRH deficiency is clinically heterogeneous and may occur with variable reproductive and non-reproductive phenotypes. One such characteristic, the sense of smell, differentiates congenital GnRH deficiency into two the variants. Some patients exhibit a normal sense of smell while others have impaired olfaction with a poor or absent sense of smell (anosmia) – termed Kallmann syndrome (KS). Olfactory acuity exists on a spectrum with approximately a third of patients being anosmic (31.5%), hyposmic (33.6%), or normosmic (34.9%) (Lewkowitz-Shpuntoff et al., 2012). Interestingly, this subtle clinical finding provides clues into the pathopysiology of this rare cause of infertility.

Pathophysiology of Congenital GnRH Deficiency

Reproductive fitness is a fundamental component of species survival and puberty is a critical developmental process leading to fertility. In higher vertebrates and mammals, reproductive capacity is an endocrine function driven by the coordinated action of the hypothalamic-pituitary-gonadal (HPG) axis. Pulsatile secretion of GnRH from the hypothalamus stimulates the release luteinizing hormone (LH) and follicle stimulating hormone (FSH), collectively referred to as gonadotropins, from the anterior pituitary (adenohypophysis) which enter the bloodstream and circulate peripherally, stimulating sex steroid production and gametogenesis in the gonads. The so-called pilot light of reproduction is GnRH, a decapeptide produced by a relatively small population of neurons in the hypothalamus (Balasubramanian et al., 2010). During embryologic development, these GnRH neurons undergo a remarkable migration from the rudimentary nose (olfactory placode) along olfactory nerves across the base of the skull (cribriform plate) into the forebrain (arcuate nuceus) where they aggregate and secrete GnRH in a coordinated fashion (Wray, 2010). This developmental link between the reproductive and olfactory system observed in Kallmann syndrome was first noted in 1856, by Maestre de San Juan who documented this association in a patient with absent olfactory bulbs and hypogonadism (Maestre de San Juan, 1856). His seminal observation was followed by Franz Kallmann in the 1940s, who reported 3 affected families with anosmia and hypogonadism (Kallmann, 1944) as well as by noted Swiss anatomist, Georges de Morsier, who reported on "dysplasia olfactogenitale" (de Morsier, 1963).

Each of these early investigators noted findings indicating that disruption of GnRH neuron ontogeny can underlie problems of puberty and reproduction. Adding further complexity to the neuroendocrine control of reproduction is the fact that the activity of the HPG axis varies across development (Bianco & Kaiser, 2009). The axis is driven *in utero* by maternal

hormones and then is active in a brief neon-natal window referred to as mini-puberty (Grumbach, 2005) prior to falling into a quiescent period during childhood. Then, puberty is initiated with a re-activation of the HPG axis. This initially occurs with sleep-entrained GnRH pulses (Boyar et al., 1974). As puberty progresses, these nocturnal episodes lengthen into daylight hours and ultimately occur around the clock. However, there is wide variation in the timing and onset of puberty and it is under the influence of numerous environmental and genetic influences (Nathan & Palmert, 2005). Disruption of this developmental of this GnRH network can result in congenital hypogonadotropic hypogonadism (CHH) and failure to initiate puberty (Bianco & Kaiser, 2009). As such, the term CHH can be used to encompass both normosmic and hyposmic/anosmic forms of GnRH deficiency while differentiating it from other GnRH deficient states such as functional causes of hypogonadotropic hypogonadism or constitutional delay of growth and puberty (Palmert & Dunkel, 2012).

To date more than a dozen different genes have been identified in association with CHH (Bouligand et al., 2009; Chan et al., 2011; Y. M. Chan et al., 2009; Clement et al., 1998; Cole et al., 2008; de Roux et al., 2003; de Roux et al., 1997; Dode et al., 2003; Dode et al., 2006; Falardeau et al., 2008; Fischer-Posovszky et al., 2010; Franco et al., 1991; Gianetti et al., 2010; Hanchate et al., 2012; Hardelin et al., 1992; Jongmans et al., 2009; Kim et al., 2010; Kim et al., 2008; Layman et al., 1998; Legouis et al., 1991; Miura, Acierno, & Seminara, 2004; Muscatelli et al., 1994; Pitteloud et al., 2006; Pitteloud et al., 2007; Seminara et al., 2003; Topaloglu et al., 2009; Topaloglu et al., 2012; Tornberg et al., 2011; Trarbach et al., 2010; Young et al., 2012; Zanaria et al., 1994) (Table 1).

However, despite these advances only approximately 65% of cases can be explained by known genetic loci (Sykiotis et al., 2010).

Table 1
Genetic loci associated with CHH

gene	year identified	references
KAL1	1991	Franco et al., 1991; Legouis et al., 1991; Hardelin et al., 1992
NROB1 (DAX1)	1994	Muscatelli et al.,1994; Zanaria et al., 1994
GNRHR	1997	de Roux et al., 1997; Layman et al., 1998
LEPR	1998	Clement et al., 1998
KISS1R (GPR54)	2003	de Roux et al., 2003; Seminara et al., 2003
FGFR1	2003	Dode et al., 2003; Pitteloud et al., 2006
NELF	2004	Miura et al., 2004; Pitteloud et al., 2007
PROK2	2006	Dode et al., 2006; Cole et al., 2008
PROKR2	2006	Dode et al., 2006; Cole et al., 2008
FGF8	2008	Falardeau et al., 2008; Trarbach et al., 2010
CHD7	2008	Kim et al., 2008; Jongmans et al., 2009
TAC3	2009	Topaloglu et al., 2009; Gianetti et al., 2010
TAC3R	2009	Topaloglu et al., 2009; Gianetti et al., 2010
GNRH1	2009	Bouligand et al., 2009; Chan et al., 2009
LEP	2010	Fischer-Posovszky et al., 2010
WDR11	2010	Kim et al., 2010
HS6ST1	2011	Tornberg et al., 2011
KISS1	2012	Chan et al., 2011; Topaloglu et al., 2012
SEMA3A	2012	Hanchate et al., 2012; Young et al., 2012

Characteristics and Sequelae of CHH

In addition to being a rare disorder characterized by genetic heterogeneity, CHH is also clinically variable in presentation (Table 2). It exists on a spectrum of disease severity from the so-called fertile eunuch phenotype (Pitteloud et al., 2001) to cases of spontaneous reversal (Raivio et al., 2007) to significant congenital anomalies including cleft lip/palate (Molsted, Kjaer, Giwercman, Vesterhauge, & Skakkebaek, 1997) and severe syndromic cases (Ballabio et al., 1989). The medical management of CHH primarily focuses hormonal therapy to induce secondary sexual characteristics and if desired, fertility. Cases of spontaneous reversal in both severe and mild forms of CHH

Table 2
Phenotypes associated with (CHH)

young looking (age > appearance)	anosmia/hyposmia	cleft lip/cleft palate (also high, arched palate)
eye anomalies (i.e. coloboma, oculomotor problems)	ear anomalies (i.e. malformed auricles)	sensorineural hearing loss
dental agenesis (hypodontia)	cryptorchidism (unilateral or bilateral)	microphallus
digit anomalies (i.e. clinodactyly, syndactyly)	synkinesia (mirror movements)	renal agenesis
obesity	skeletal problems (i.e. scoliosis)	osteopenia/osteoporosis

Note: Mitchell et al., 2011

have been reported in the literature (Cole et al., 2008; Pitteloud et al., 2005; Raivio et al., 2007; Raivio et al., 2009; Tornberg et al., 2011). It is estimated that approximately 10% of patients will be undergo a reversal (Raivio et al., 2007) yet there are no identified predictors to date. Further, as this is a relatively recently reported phenomenon, it not yet well understood and we do not know if these patients may revert to hypogonadal states. As such, the vast majority of patients diagnosed require lifelong hormone therapy (Han & Bouloux, 2010; Young, 2012).

Treatment can have clinical importance beyond the reproductive years, as sex steroids (i.e. testosterone and estradiol) play important roles in bone mass formation and preservation. Because CHH patients lack the surge of gonadotropins and increased sex steroid levels of puberty, they lose out on a critical period of bone formation and are at increased risk for developing osteoporosis (low bone density). With appropriate long-term hormone treatment this heightened risk for fractures can be ameliorated (Dode & Hardelin, 2009; Seminara et al., 1998; Waldstreicher et al., 1996; Young, 2012). However, if untreated or if treatment is stopped, patients rapidly become hypogonadal (with very low sex steroid levels) which is a

risk factor for osteoporosis in both men and women (Finkelstein et al., 1987; Potap et al., 1987; Laitinen et al., 2012).

Additionally, for CHH men, androgen therapy (i.e. testosterone replacement) has well-documented beneficial effects on maintaining muscle and fat-free (lean) body mass (Bhasin et al., 1997; Wang et al., 2004). Further, several meta-analyses have demonstrated an association between low serum testosterone levels and the metabolic syndrome and diabetes (Ding et al., 2006, Coronoa et al., 2011; Brand et al., 2011). Further, acute withdrawal of treatment from CHH men induces increased fasting insulin levels and insulin resistance within two weeks (Yialamas et al., 2007). Thus, lack of or inadequate androgen replacement may place CHH men at increased risk for developing the metabolic syndrome and potential cardiovascular morbidity. As such, adequate treatment and close monitoring is warranted to limit these potential sequelae (Laitinen et al., 2012)..

Diagnosis and treatment of CHH

The first issue on treating CHH is obtaining an accurate diagnosis. By definition, CHH involves abnormally low levels of serum gonadotropins (LH & FSH) as well as low sex steroids (testosterone [T], estradiol [E2]) and may result from either abnormal GnRH release from the hypothalamus or by defective responsiveness of the pituitary gonadotpropes (Bianco & Kaiser, 2009; Brioude et al., 2010; Mitchell, Dwyer, Pitteloud, & Quinton, 2011). Broadly CHH patients fall into three categories, about 51% are normosmic, 39% have disturbed olfaction or no sense of smell (KS), and the remaining 10% have syndromic forms of the disorder (Young, 2012). Syndromic forms are often identified in pediatric settings as the signs are evident prior to pubertal onset and may include other metabolic or endocrinopathies, neurologic problems, and/or congenital malformations (Farooqi et al., 2007; L. Lin et al.,

2006; Netchine et al., 2000; Pinto et al., 2005; Reynaud et al., 2006; Rottembourg et al., 2008). However, a hallmark characteristic of CHH is incomplete-absent puberty and the primary differential diagnosis for this rare disorder is the relatively common diagnosis of constitutional delay of puberty, which is simply an extreme variant of the normal timing and onset of puberty (Nathan & Palmert, 2005; Palmert & Dunkel, 2012; Sedlmeyer & Palmert, 2002). As such, many CHH adolescent males presenting with abnormal pubertal development (i.e. absent puberty after 14 years of age) may be missed as the clinical presentation is assumed to be a variant of pubertal timing or delayed puberty. Indeed, labeling patients as "late-bloomers" may be a key reason why the vast majority of CHH patients experience delays in diagnosis and frequently present to adult providers as adults with complaints of aberrant puberty and hypogonadotropic hypogonadism (Young, 2012). This delay in receiving an accurate diagnosis is not uncommon in rare diseases (EURORDIS, 2009) yet the consequences can be psychologically and emotionally crippling for patients who are essentially adults living in a preadolescent body.

Further complicating the timely and accurate diagnosis is the fact that CHH is a diagnosis of exclusion, meaning that the clinician must "rule-out" other potential causes (Table 3) via clinical examination, biochemical profiling, radiologic studies, and dynamic endocrine testing (Young, 2012). This process can be lengthy and unsettling for patients, yet once the proper diagnosis is reached there are a number of effective treatments for CHH. Based on goals for treatment, therapeutic options for both male and female CHH patients falls into one of 2 categories; sex steroid replacement to induce secondary sexual characteristics or hormonal treatment to induce fertility. As this project focuses on CHH males, a brief overview of available treatment options is provided.

Table 3
Differential diagnoses and rule-out causes of GnRH deficiency

Acquired Forms	Syndromic Causes
central nervous system tumor	CHARGE syndrome
Pituitary apoplexy	Prader-Willi syndrome
head trauma	Bardet-Biedl syndrome
Radiation (brain/pituitary)	combined pituitary hormone deficiency
medication-induced	septo-optic dysplasia
	leptin deficiency/resistance
Functional causes	**Systemic diseases**
malnutrition/malabsorption	hemochromatosis
eating disorders	sarcoidosis
hypothyroidism	histiocytosis
hyperprolactinemia	
diabetes mellitus	
Cushing's disease	

Note: King & Hayes, 2012: Pallais et al., 2010; Young 2012

Treatment to induce normal changes of puberty

Inducing secondary sexual characteristics in males is achieved via testosterone replacement therapy (TRT) which is available in a variety of forms (Table 4) (T.S. Han & P.M. Bouloux, 2010). TRT induces a number of changes which are normally evident in puberty including increased height, development of muscle mass, deepening of the voice, virilization with growth of facial, axillary, and pubic hair as well as an increase in penis size. These body changes are accompanied by increased secretion of oil and sweat from the sebaceous glands resulting in acne and body odor. The World Health Organization (WHO), U.S. National Institutes of Health (NIH), and the U.S. Food and Drug Administration (FDA) all concur that the goal of TRT is to replace serum levels as close to physiologic levels as possible in order to mirror developmental changes in age-matched peers (Nieschlag et al., 1992).

Table 4
Testosterone preparations

route of administration	**frequency**	**benefits**	**drawbacks**
transdermal (gel)	daily	self-administered, non-invasive	local reaction, transferability
transdermal (patch)	daily	self-administered, non-invasive	local reaction, skin irritation
buccal	twice daily	self-administered, non-invasive	local reaction, frequency of use
intramuscular injection	every 2-4 weeks	long-acting, can be self-administered	invasive, polycythemia risk
intramuscular injection	every 3 months	long-acting	invasive, polycythemia risk, requires provider injection
subdermal implant	every 6 months	long-acting	invasive, polycythemia risk, extrusion, fibrosis, requires outpatient surgical procedure

Note: Edelstein & Basaria, 2010; Gooren, 2009; Zitzmann & Nieschlag, 2000

Initially, TRT is a balance between stimulating growth (increased height) and avoiding premature epiphyseal closure caused by high serum testosterone levels and resulting in a shorter terminal height (Palmert & Dunkel, 2012). Thus, doses are gradually escalated, yet this can be a source of frustration for patients as they may be eager to "catch up" to their peers or "look normal". If this is not addressed in appropriately timed anticipatory guidance, the patient may have inappropriate expectations for treatment resulting in negative experiences or feelings related to the regimen. In addition to developing secondary sexual characteristics, TRT also aims to improve bone mineralization and it can have a significant positive impact on patients in terms of improved energy levels and developing adequate sexual functioning such as increased libido, frequency of erections, morning erections, and capacity for masturbation and penetrative intercourse (Han & Bouloux, 2010; Young, 2012). While these changes would presumably impact quality of life, few studies have directly examined the impact of starting TRT in CHH men.

A recent study of 39 young men with CHH demonstrated increased sexual dysfunction, more anxiety and depressive symptoms, and lower quality of life scores compared to age matched peers (Aydogan et al., 2012). The sexual dysfunction, anxiety, and depression ratings improved with TRT and after 6-moths, the CHH men scored no differently than their age matched eugonadal peers. Notably, while virtually all subcategories of the quality of life measures improved, the HH men on treatment still had significantly lower scores related to general health, vitality/energy, and physical and emotional role difficulties. These data suggest that normalizing the serum hormone levels does not completely ameliorate the biopsychosocial effects the CHH has on patients' quality of life. Such findings are in line with past research demonstrating that psychological morbidity persists in patients successfully treated for a number of endocrinopathies (Sonino et al., 2004; Sonino, Ruini, et al., 2007; Sonino, Tomba, & Fava, 2007)

Long term TRT is efficacious in maintaining physiologic testosterone levels, energy level, proper sexual function, and promoting lean muscle mass and preserving bone density (Gooren, 2009; Zitzmann & Nieschlag, 2000). However, TRT has no effect on testicular development and the testes will remain small (infantile in some cases) and this can be stressful and a source of concern for patients when they become sexually active (Han & Bouloux, 2010). Indeed, some authors have noted the atrophic testes and severely diminished phallus size (often associated with CHH) can have serious negative effects on self confidence and psychosexual development (Bouvattier et al., 2012). Further, as TRT does not induce fertility, some have suggested that infertility may have additional deleterious psychological and emotional effects on patients (Aydogan et al., 2012). However, patient perceptions of these issues have yet to be explored.

Treatment to induce fertility

Treatments to induce testicular development and fertility in CHH men have been available since the 1980s. One approach is to replace the absent hypothalamic hormone (GnRH) via microinfusion pump to induce physiologic pulses of GnRH which in turn stimulate the release of endogenous LH and FSH (Buchter, Behre, Kliesch, & Nieschlag, 1998; Hoffman & Crowley, 1982). Alternatively, exogenous gonadotropins in the form of human chorionic gonadotropin (hCG) (Finkel, Phillips, & Snyder, 1985; Vicari et al., 1992), or combined gonadotropin therapy (FSH+hCG) (Bouloux et al., 2003; Matsumoto et al., 2009) may be utilized. Outcomes related to testicular growth and development of fertility (evidence of sperm in the ejaculate) are variable, and poorer responses have been noted in patients with more severe clinical presentations such as small/prepubertal testicular volume, a history of cryptorchidism (undescended testes at birth), and/or low markers of sperm production (serum inhibin B levels) (Liu et al., 2009; Miyagawa et al., 2005; Pitteloud et al., 2002; Warne et al., 2009). Notably, there is no significant advantage of one approach over another as nearly equivalent outcomes are observed (Buchter et al., 1998; Liu et al., 2009). While treatment may be required for 18-24 months to achieve optimal results (Buchter et al., 1998; Burris, Rodbard, Winters, & Sherins, 1988), these are highly effective treatments with approximately 80% of patients developing a potential for fertility with sperm in the ejaculate (Liu et al., 2009; Miyagawa et al., 2005; Pitteloud et al., 2002; Warne et al., 2009). Despite the high success rates for developing sperm in the ejaculate, many men achieve maximal sperm counts that are far below the range which is considered normal by the WHO (Cooper et al., 2010). However, this does not preclude fertility as it is known that CHH men can conceive naturally despite low sperm counts (Burris, Clark, Vantman, & Sherins, 1988).

Potential side effects and monitoring of treatment

The available TRT and fertility treatments available for CHH men are effective and overall very well-tolerated. However, there are potential negative effects of TRT (sleep apnea, cardiovascular risk, alteration of lipid profile, fluid retention, benign prostate hypertrophy, and risk for prostate cancer). Yet these are typically not of clinical relevance as long as serum testosterone levels are maintained within a normal physiologic range (Rhoden & Morgentaler, 2004). Some adverse effects are related to the mode of delivery, such as higher rate of erythrocytosis (elevated levels of red blood cells do to the erythropoetic effect of testosterone) in men receiving injections, and higher rates of local reaction in men receiving transdermal preparations (patch or gels) (Rhoden & Morgentaler, 2004). Rapid changes in serum hormone levels can disrupt the balance of androgens and estrogens resulting in development of glandular breast tissue referred to as gynecomastia. This can be a negative side effect of TRT and occurs quite frequently with gonadotropin therapy (i.e. hCG injections) to induce fertility (Boyar et al., 1973). Other potential drawbacks to fertility inducing treatments include the extreme cost, the duration of treatment required to attain fertility, the invasiveness of the treatment (requiring either injections given every other day or wearing a microinfusion pump attached to a subcutaneous needle), and the limited expertise in treating rare patients with these specialized treatments.

Psychosocial aspects of CHH

Rare genetic diseases are often associated with psychological burden and negative emotional and psychosocial effects (Cohen & Biesecker, 2010; McAllister et al., 2007). Further, roughly two-thirds of CHH patients have impaired sense of smell (Lewkowitz-Shpuntoff et al., 2012), an impairment that is in and of itself associated with higher ratings of social insecurity and depressive symptoms (Croy, Negoias, Novakova, Landis, & Hummel, 2012). While sense of smell is something indiscernible to others, the absent pubertal development of CHH is

outwardly evident and this visible difference from their peers often lasts throughout their teen years. Puberty is a process characterized by numerous physiologic, psychosocial, and emotional changes and accompanied by the developing self-concept and disruption of puberty can carry a psychological burden (Palmert & Dunkel, 2012). Some of the psychological consequences of delayed puberty in late maturing 14-16 year-old boys include body image concerns, low self esteem, social isolation and many experience teasing or bullying (Golub et al., 2008; Kaplowitz, 2010; Rosen & Foster, 2001). Further, victimization and bullying are important and common risks for depression in adolescents (Thapar, Collishaw, Pine, & Thapar, 2012) and late maturing boys are more dissatisfied with their body image, more likely to engage in binge eating, and less sexually active than boys who underwent an average timing of puberty (Michaud, Suris, & Deppen, 2006). This constellation of having a rare disease which can induce feelings of isolation and alienation combined with the impact of having a very severe form of delayed puberty may contribute to a sense of social isolation, low self esteem, and negative psychological outcomes in CHH patients (EURORDIS, 2009).

There is some evidence to suggest that CHH impacts the sexual life of CHH men as the body image concerns and low self-esteem arising from pubertal failure and underdeveloped genitalia can pose a barrier to engaging in sexual activity (Bouvattier et al., 2012). Further, it has been suggested that the lack of rising sex steroid levels of puberty may have long-lasting negative effects on psychosexual development in CHH men (Huffer, Scott, Connor, & Lovice, 1964). Yet, thorough examination of the impact of these issues of quality of life and sexuality is lacking. Indeed there are only small case studies that examine these issues in a qualitative manner: a 1971 report of 13 cases from the Johns Hopkins University Hospital (Bobrow, Money, & Lewis, 1971) and a 1996 case series describing eight CHH men initiating pulsatile GnRH (Huisman, Bosch, & Delemarre vd Waal, 1996). In some instances, the

psychological burden of a lagging puberty may be compounded with the initiation of treatment as TRT therapy can rapidly normalize sexual function but may not address the physical and emotional difficulties in adapting to life as a sexual being (Aydogan et al., 2012). Some patients may be challenged to deal with the rapid changes of exogenously induced puberty such as acne, body changes, and potentially breast development (gynecomastia). As such, patients should receive anticipatory guidance and close monitoring and individual dose titration to ensure that physiologic levels are achieved to avoid potential negative side effects that may include mood swings related to rapidly changing hormone levels (Han & Bouloux, 2010). Further, CHH men diagnosed later in their 20s and 30s may face additional challenges as they learn to cope with a newfound sexuality and the increased libido and change in sexual function is a vast alteration from what they are used to feeling (Huffer et al., 1964). This dissonance may pose of barrier for adhering to treatment as the emergence of a sexual identity may be psychologically and emotionally challenging for these men.

Several publications mention the psychosocial stress related to CHH and that patients may feel self-conscious, awkward, or embarrassed because of their lagging sexual development, undeveloped genitalia, and infertility that in some cases is emotionally crippling for patients (Huffer et al., 1964; Han & Bouloux, 2010Au, Crowley, & Buck, 2011; Aydogan et al., 2012;; Bouvattier et al., 2012; Young, 2012). Previous reports from 1964, 1971, and 1996 describe in a rather anecdotal way issues with confidence, security, and poor views of physique (Bobrow et al., 1971; Huffer et al., 1964; Huisman et al., 1996). While this aspect of care maybe mentioned in the context of the approach to the patient, the significance of these psychosocial implications have not been extensively explored and it is unknown what role these may have in relation to adherence to treatment. Despite the benefits of treatment in

ameliorating health problems/risks and the availability of effective treatment options, adherence to treatment is a significant problem across therapeutic areas (WHO, 2003).

In relation to CHH, several publications make reference to individual patients being "lost to follow-up" (Pitteloud et al., 2001; Pitteloud et al., 2007; Quinton et al., 1999; Raivio et al., 2007), yet there is a notable paucity of data on adherence to treatment in this population. An early series reported in the Annals of Internal Medicine in 1964 charts the response of eight men during pubertal induction (Huffer et al., 1964). The authors poignantly note, "*There is a tendency among physicians to assume that a corrigible pathological condition ought to be corrected and that the emotional well-being of the patient will improve concomitantly with his physical condition*" (p. 265). However, the carefully depicted cases suggest otherwise; two men (25%) ceased treatment and medical follow up, while the other six men struggled with issues of anxiety, depression, and social difficulties as they negotiated the changes of adolescence in the 3rd to 5th decade of life. More recently, a report examining bone health in a cohort of 26 Finnish CHH patients indicated that nine patients (35%) had long periods of non-adherence to therapy with treatment pauses exceeding five years (Laitinen et al., 2012). In summary, despite the availability of effective treatments, there are seemingly other issues diminishing CHH patients' self-care and health seeking behavior.

Addressing the Challenges to Health in CHH Patients

As previously discussed, patients with rare diseases face a multitude of livelong challenges which place them within the framework of chronic care and health disparities (Holtzclaw Williams, 2011). Patients with rare diseases, including CHH, experience delays in getting an accurate diagnosis, and have difficulty identifying providers with expertise in treating their condition which can induce feelings of isolation and alienation (EURORDIS, 2009). When combined with the psychosocial stressors described above, these factors may impede

adherence to treatment which has important health ramifications for patients with chronic disorders. Patients with chronic conditions provide approximately 95% of their care (Funnell & Anderson, 2000), and the daily decisions people make regarding their health can have a huge impact on patient outcomes and quality of life. Activating patients to develop and practice self-care is a means to empower patients and facilitate health promoting behaviors that are critical for managing chronic conditions (Simmons, 1990). Nurses play a crucial role in guiding and teaching patients to perform self-care and in delivering what the WHO terms health promotion, the process of enabling people to overcome health challenges and increase control over their environment to achieve greater health (WHO, 1986). This definition, is intertwined with empowerment, a central theme in health promotion, health equity, and chronic disease management which are directly relevant to patients with rare diseases (Marmot, 2007).

In the realm of common chronic diseases such as diabetes, the shortfall between what is known about managing the condition and its complications and what is actually practiced has been well documented (Glasgow, 2003). This has led to the adoption of a number of quality improvement initiatives including the implementation of evidence-based practices and a shift from a provider-centered compliance approach to a patient-centered empowerment (Glasgow & Anderson, 1999; Wagner, Austin, & Von Korff, 1996a, 1996b). One integrated approach, the Chronic Care Model (CCM), was developed to facilitate interactions between informed, activated patients and a prepared, proactive care team that includes physicians, nurses, social workers, dieticians/nutritionists, therapists and others and is now widely used (Bodenheimer, Lorig, Holman, & Grumbach, 2002). This collaborative paradigm emphasizes members of the care team as health coaches who are critical for helping the patient to gain knowledge and develop self-care skills to become confident, active participants in their care. Nurses play a

key role in providing self management support, bridging gaps between the patient and provider, assisting in the navigation of the healthcare system, and providing continuity of care (Bennett, Coleman, Parry, Bodenheimer, & Chen, 2010; Bodenheimer et al., 2005; Ghorob & Bodenheimer, 2012). Such nursing sensitive, patient-centered targets for intervention help patients become more informed and activated and are effective in improving a number of patient outcomes (Wagner et al., 2001).

Interventions aimed at self management support include traditional patient education as well as training in problem solving skills and are the component of the CCM most frequently associated with improved outcomes (Pearson, Mattke, Shaw, Ridgely, & Wiseman, 2007) . A significant amount of CCM literature has focused on diabetes self-care. A meta-analysis of 31 studies demonstrated that self-management support was associated with improved glycemic control (Norris, Lau, Smith, Schmid, & Engelgau, 2002) and a more recent meta analysis of group-based programs also improved knowledge as well as glycemic measures (Steinsbekk, Rygg, Lisulo, Rise, & Fretheim, 2012). These findings were also supported by Cochrane systematic reviews of both individual and group interventions in type-2 diabetes (Deakin, McShane, Cade, & Williams, 2005; Duke, Colagiuri, & Colagiuri, 2009). Nurses have also demonstrated a key role in planned visits, an aspect of the CCM in which time is dedicated to key patient education topics, review medications, and address other patient concerns (Bodenheimer, 2005b). A systematic review of 41 studies evaluating the role of planned visits demonstrated that they are such interventions are effective in improving glycemic control and that nurses play central role in this process and can replace physicians in delivering many aspects of diabetes care with the proper training and support (Renders et al., 2001). Notably, the common denominator in successful implementation of patient-centered approaches to care

includes a central role for nurse care managers within the CCM (Aubert et al., 1998; Glasgow et al., 2001; Sadur et al., 1999).

As demonstrated by the systematic reviews and meta-analyses described above, the CCM utilizes self management training, planned visits, and case management to develop informed, activated patients, achieve sustained continuity of care, and improved health outcomes (Bodenheimer, 2005a). Patients' satisfaction with care and positive patient-provider interactions are important determinants for self care that can either promote or undermine patient self-management (Flocke, Miller, & Crabtree, 2002; Glasgow et al., 2001; Little et al., 2001). Recently, there is a growing movement towards a chronic care model for patients with rare diseases that is patient centered and includes them as informed, involved and interactive partners in the health care team (Burton, Murphy, & Riley, 2010). As such, one might anticipate that the benefits of applying the collaborative approach of the CCM to rare disease patients would be a patient-centered approach which empowers patients to develop expertise in self management as well as enhanced continuity of care.

Nursing and patient-centered care.

At the core of the CCM, is the notion of patient-centered care involving an ongoing collaborative process between an empowered, activated patient and the care team (Bodenheimer, Lorig, et al., 2002; Bodenheimer, Wagner, & Grumbach, 2002). Patient-focused care integrates elements of patient education, self-care, and evidence-based models of practice and distills them into interventions aimed at improving communication and developing partnerships with patients, providing physical care, and enabling health promoting activities (Bauman, Fardy, & Harris, 2003; Irwin, 2004; Irwin & Richardson, 2006). Nursing fits well with patient-focused approaches as they draw on roles that nurses have traditionally provided leadership in: patient education, advocacy, developing self-care, enhancing coping

skills, enabling empowerment, and promoting self-efficacy in patients. In patient-focused care, the role of healthcare provider is no longer that of the professional expert who gives instructions and makes the decisions. Rather, they are a coach or a guiding advisor helping the patient navigate their health according to personalized goals (Bennett et al., 2010; Greenhalgh, 2009). This paradigm shift allows for a shared decision-making process focused on informing, assisting, and activating patients towards enhanced self-management their condition (Barlow, Wright, Sheasby, Turner, & Hainsworth, 2002; Bodenheimer, Lorig, et al., 2002).

Patient-centered care dramatically reframes patient involvement, shifts the role of the healthcare professional, and redefines successful health outcomes (Greenhalgh, 2009). Nurses have been leaders in developing chronic disease self-management training programs that build self-efficacy and improve patient outcomes (Marks, Allegrante, & Lorig, 2005a, 2005b). Such programs acknowledge patient expertise and redefine expectations related to care and it has been posited that this challenge to biomedical superiority has posed barriers to more widespread implementation of patient-centered programs (Lawn, McMillan, & Pulvirenti, 2011; Thorne, Ternulf Nyhlin, & Paterson, 2000). Patients with rare diseases are often forced to become their own experts due to the lack of expert care. Indeed, the vast majority of these patients seek information on their own, and with time, the relative expertise of the health professional diminishes. Further, healthcare providers' ability to accept patients as informed, interactive, and involved partners in the process has significant impact on the patient experience (Budych, Helms, & Schultz, 2012). Not surprisingly, information exchange is an essential step in meeting the care needs of rare disease patients and knowledge sharing improves patient satisfaction (Hannemann-Weber, Kessel, Budych, & Schultz, 2011). One way to address the unmet health needs of these patients is through patient-centered

empowerment approaches that develop knowledge and expertise enabling self-management that is critical for chronic conditions (Ho, Berggren, & Dahlborg-Lyckhage, 2010).

The complexity of rare diseases poses many challenges, yet these hurdles may be overcome by creative use of interdisciplinary teams that include patients. Different health care providers have different expertise and patients have an intimate and sophisticated understanding of their own disease. Therefore, assembling a team with diverse knowledge, abilities, and skills may lead to idea generation and implementation of approaches that will enhance patient outcomes (van Knippenberg, 2006; Wensing, Wollersheim, & Grol, 2006). Much like the successful application of the CCM to diabetes, multidisciplinary teams including medicine, nursing, social work, and others have been shown to be effective in providing comprehensive patient-centered care for a number of genetic disorders (Baker, Crudder, Riske, Bias, & Forsberg, 2005; Burton et al., 2010; Evatt, 2006; Grosse et al., 2009) and appears to hold relevance for rare disease patients.

Theoretical Foundations for Nursing Practice and Relevance to Rare Disease Patients

Consistent with nursing's unique contributions to multidisciplinary teams and CCM (Bodenheimer et al., 2005), the field of nursing has utilized a number of theoretical foundations to better understand health and behavior. Nursing's integrated and individual definition of health is rooted in the philosophy of postmodernism (Reed, 1995). Postmodernism is iconoclastic in that it deconstructs the reductionism of empiricism. Rather than identifying one objective reality, the focus is on multiple meanings. It is pluralistic in that it accepts multiple realities and truths. In the context of health, this is important as it places the definition of health not with the professional expert, but rather it includes the viewpoint and experiences of the patient through their own subjective lens. This notion is

fundamental to a core tenet of nursing, respect. By accepting multiple truths, the nurse removes the judgment that one reality is superior to another. This has a leveling effect for the power dynamic and facilitates shared decision making as it removes blame and provides validity for each participants' views. The postmodernism appreciation of the absence of one objective reality is foundational to developing approaches to patient-centered care as it recognizes that the perspective of the professional healthcare provider is not the only valued point of view.

Further, given the unique challenges faced by patients with rare diseases, innovative, individualized approached to care and patient centered care teams are essential to address the complex needs of these patients (Hannemann-Weber et al., 2011). Building on the foundation of respect for individuals and the appreciation of different perspectives, nursing places the definition of health in the context of the individual and engages in activities with individuals, families, and communities to create optimal conditions for improving health and well-being and nursing's unique mix of skills and competencies will inevitably play a key role in developing and implementing patient focused approaches to care that are built to value both health promotion and patients' involvement in a context of long lasting disease (Sibbald, Shen, & McBride, 2004). Accordingly, it follows that nursing has played an important role in implementing the CCM (Bodenheimer et al., 2005) which aims to activate patients for enhanced self-management and self-care of their chronic health condition.

Pender's Health Promotion Model (HPM)

One of the nursing models that has been utilized to understand and predict health seeking behaviors is the Health Promotion Model (HPM) of Nola Pender (Pender, Murdaugh, & Parsons, 2010). The HPM model is based on an earlier model, the Health Belief Model (HBM), which was developed to examine patient health behaviors (Janz & Becker, 1984).

The HBM incorporated the interrelated concepts of modifying factors, cognitive-behavioral factors, and other variables influencing likelihood of action creating a model to understand how individuals protected their health. At the core of this model is the idea that the fear or threat of a disease is a motivator for positive health behavior, essentially defining it as a disease avoidance model (Galloway, 2003). In contrast, Pender's HPM is not focused merely on health protection or disease avoidance, but rather places health within a nursing perspective and focuses on achieving higher levels of wellness and self-actualization. Pender's HPM concentrates on the interactions between three broad areas that flow linearly towards health promoting behavior: i) individual characteristics and experiences, ii) behavior-specific cognitions and affect, and iii) behavioral outcomes (Pender, Murdaugh, & Parsons, 2010. This model is patient-centered and places the definition of health and the importance of health within the value scale of the individual (Figure 3).

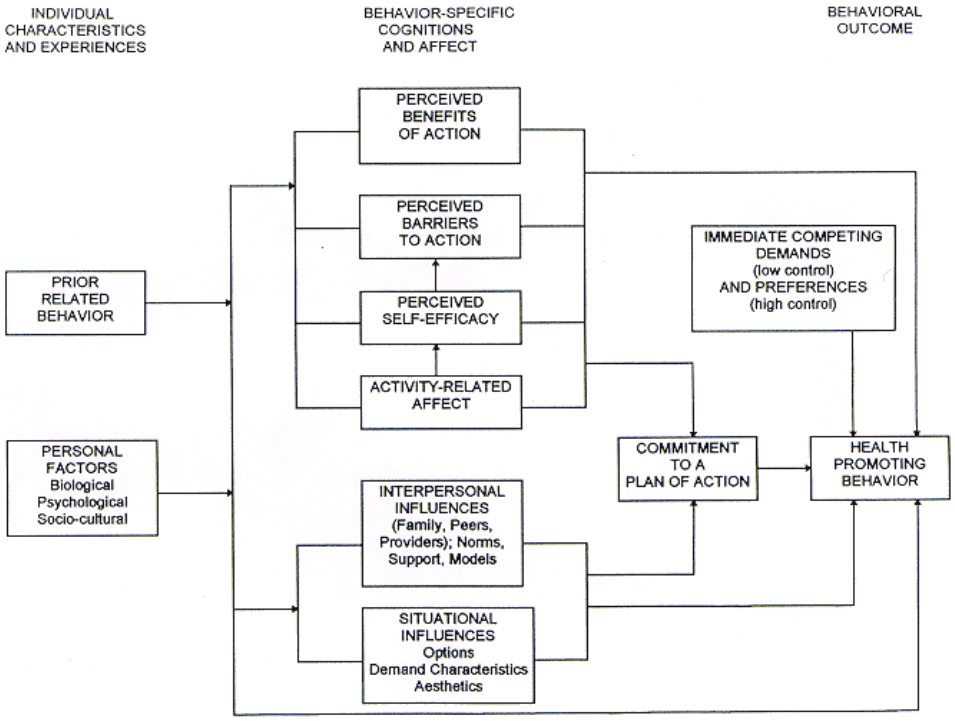

Figure 3. Pender's Revised Health Promotion Model. Reprinted from *Health Promotion in Nursing Practice* (p. 45), by Pender, N. J., Murdaugh, C. L., & Parsons, M. A., 2010, Upper Saddle River, NJ: Prentice Hall.

Given the holistic and multidimensional view of the individual, the HPM has been used to examine numerous biopsychosocial influences impacting health promoting behavior (outcomes) and has been used as a model to guide effective nursing interventions (Gillis, 1993).

Theoretical underpinnings of the HPM

The HPM is rooted in the humanistic psychology of Abraham Maslow (Maslow, 1999), the expectancy value theory of Normal Feather (Feather, 1982), and in Social Cognitive theory of Albert Bandura (Bandura, 1986). Similar to Maslow's hierarchy of needs, the HPM recognizes that basic needs must be met for patients to aspire and move towards higher levels of health and self-actualization. Feather proposed that in situations involving a degree of choice, action and behavior are strongly influenced by the expectation of being successful and the value placed on the desired outcome, meaning that it is something useful or enjoyable (Feather, 1982). In terms of understanding and predicting human behavior, the HPM is grounded in Bandura's Social Learning Theory (Social Cognitive Theory). In the Social Learning Theory, the locus of control is within the individual. Bandura posited that individuals are self organizing and that personal factors (biological, cognitive, and affective), behavior, and the environment all interact. From this dynamic interaction, individuals derive a personal sense of being able to effectively interact with and transform their environment, the concept of self-efficacy (Bandura, 1986).

The HPM posits that individuals will actively seek to regulate their own health behavior and that health is the actualization of human potential attained through goal-directed behavior. Effective self-care, satisfying relationships, and harmony with the environment are key elements of the HPM holistic view of health. Further, the model recognizes the complexity of individual characteristics and how both cognitive and affective aspects of experiences can

either enhance self-efficacy, and action towards health promoting behaviors, or alternatively, create barriers to action. Such positive/negative factors are the primary motivators for health promoting behaviors and include subjective perceptions related to the definition and importance of health, perceived control over health, current health status, perceived self-efficacy related to health, as well as perceived benefits and barriers to health promotion behaviors (Pender, Murdaugh & Parsons, 2010)). The desired outcome in the HPM is action and behaviors which improve health and well-being, functional abilities, and ultimately improved quality of life. These positive health seeking behaviors are the targets for nursing intervention.

How has the HPM been used in nursing research?

The HPM is multidimensional and recognizes a variety of interrelated factors exerting direct and indirect influences on health behavior. A core tenet of the model is the spectrum of disease states ranging from disease to well-being which is ever-changing. This fluid state of health fits well with the nursing process of assessing, analyzing, planning, implementing, and evaluating which is cyclic, dynamic, and goal-oriented (Faust, 2002). And like the nursing process, the HPM is flexible as it can be applied to individuals, families, or communities. Further, the model is useful as a framework for assessment and as a means to evaluate interventions to address an identified need (McClune, 2009; Walker et al., 2009) and has demonstrated predictive abilities in a variety of settings (Hong, Lusk, & Ronis, 2005; Lusk, Ronis, & Hogan, 1997; Ronis, Hong, & Lusk, 2006; Stuifbergen & Becker, 1994; Weitzel & Waller, 1990).

The HPM has been applied to examine specific disease avoidance/health protecting behavior such as exercise (Eden, Orleans, Mulrow, Pender, & Teutsch, 2002; Garcia et al., 1995; Shin, Yun, Pender, & Jang, 2005; Wu & Pender, 2002; Wu, Pender, & Yang, 2002), smoking

cessation (Kelley, 2009; Wynd, 1999), and injury protection (Coppens & McCabe, 1995; Hong et al., 2005; Lusk et al., 1997; Lusk, Ronis, Kerr, & Atwood, 1994; McCullagh, Lusk, & Ronis, 2002; Ronis et al., 2006). Beyond its application in understanding disease avoidance, it has also been useful in identifying attributes and variables associated with health promoting behaviors and lifestyles in wide-ranging groups of patients (Ahijevych & Bernhard, 1994; Duffy, 1993; Duffy, Rossow, & Herandez, 1996; Eschiti, 2008; Frank-Stromborg, Pender, Walker, & Sechrist, 1990; Kerr & Ritchey, 1990; Kwong & Kwan, 2007; Lusk, Kerr, & Ronis, 1995; May & Rew, 2010; Padula & Sullivan, 2006; Stuifbergen & Becker, 1994; Viau, Padula, & Eddy, 2002; Wilson, 2005; N. F. Woods, Lentz, & Mitchell, 1993).

Further, the HPM has been used to identify barriers to health promoting behavior (Mendias & Paar, 2007; Parve, 2004), the association of health promoting behaviors and quality of life (Han, Lee, Park, Park, & Cheol, 2005; Stuifbergen, 1995), and to evaluate healthcare providers' attitudes towards health promotion (Conway, McClune, & Nosel, 2007). Notably, health promotion activities have been shown to have a positive impact in patients with chronic disabling conditions (Stuifbergen, Morris, Jung, Pierini, & Morgan, 2010). Indeed, the work of Stuifbergen and colleagues have demonstrated the applicability and value of the HPM for not only understanding barriers to health promoting activities among patients with chronic health conditions, but also as a model for delivering wellness interventions to activate patients and achieve improved quality of life (Stuifbergen, 2006; Stuifbergen, Becker, Blozis, Timmerman, & Kullberg, 2003; Stuifbergen et al., 2012; Stuifbergen, Blozis, et al., 2010; Stuifbergen, Morris, et al., 2010; Stuifbergen & Rogers, 1997). As such, the HPM appears to be theoretically coherent with the CCM - wherein the objective is to link proactive healthcare teams with informed and activated patients to promote enhanced health outcomes (Wagner et

al., 1996b). Further, the HPM has been used as a framework for patient empowerment for diabetes (Ho et al., 2010). The demonstrated benefits for patients with chronic conditions and the HPM's theoretical links with concepts of self-actualization, self-efficacy, enhanced coping, and empowerment have direct relevance for patients with rare diseases making it an appropriate theoretical framework.

Purpose of Statement

The purpose of this study is to use the nursing framework of Pender's HPM in order to examine the relationship between illness perception, depressive symptoms, and adherence to treatment in male patients living with a rare disease, CHH. This needs assessment will identify areas for developing targeted nursing interventions and enhanced patient-centered approaches to care.

Implications, Nursing Significance, and Adaptation of the HPM to this Study

Nursing has played a key role in providing patient-centered approaches to care in the management of chronic conditions. Such nursing interventions are relevant for patients and families affected by rare diseases. Therefore, this needs assessment is an initial and critical step for identifying targets for nursing interventions and developing rational, empowerment based, patient-centered approaches addressing the chronic care needs of patients with rare diseases. This study will be nested within the theoretical framework of Pender's HPM as it provides a pragmatic and useful explanatory model for health behavior.

Specific Aims

This study proposes to address four specific aims, each relating to specific dimensions of the Pender's HPM in relation to men living with CHH.

Specific Aim 1: Individual characteristics and experiences.

To assess illness perceptions and depressive symptoms in men with CHH.

Specific Aim 2: Behavior-specific cognitions and affect.

To explore CHH patients' perceived barriers related to health promoting behavior.

Specific Aim 3: Interpersonal influences.

To describe the type and quality of interactions with healthcare providers.

Specific Aim 4: Behavioral outcomes/Health promoting behavior

To evaluate adherence to treatment in men with CHH.

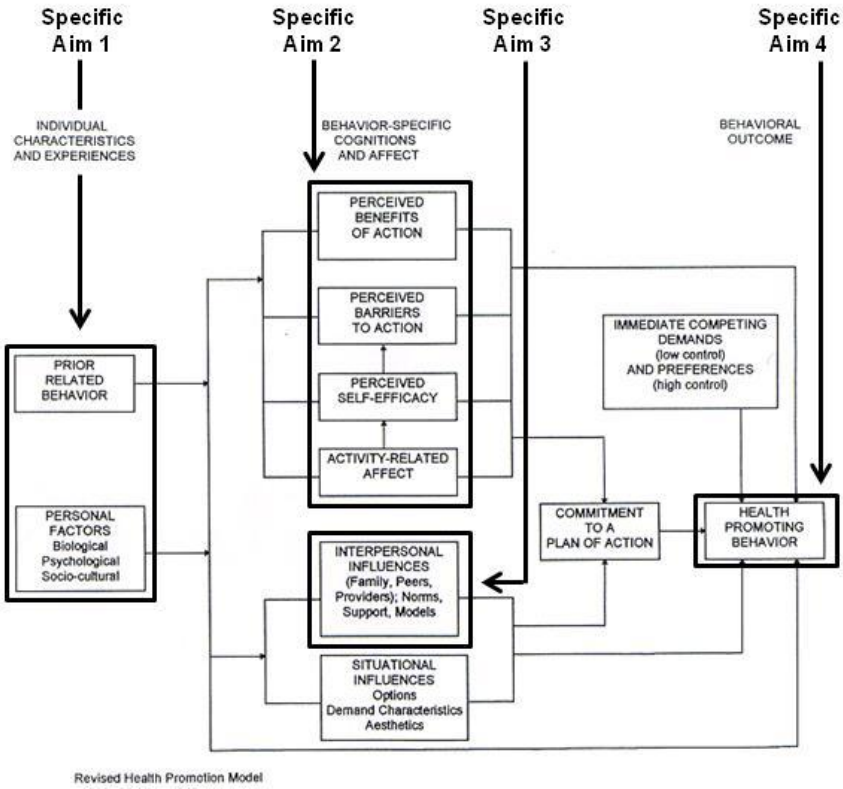

Figure 4. Theorectical schematic for the proposed study. Pender's Revised Health Promotion Model reprinted from *Health Promotion in Nursing Practice* (p. 45), by Pender, N. J., Murdaugh, C. L., & Parsons, M. A., 2010, Upper Saddle River, NJ: Prentice Hall.

Chapter III: Methods

Design

First, a descriptive, multivariate correlational needs assessment study utilizing a community based participatory research framework was used. This approach has previously been put forth as a useful research model for empowering patients and overcoming health inequities (Wallerstein & Duran, 2006). As part of a European network focused on CHH (COST Action BM1105, www.gnrhnetwork.eu) partnerships were developed with expert patients and online patient community leaders (i.e. moderators of online patient support sites) to engage stakeholders in the process of study design and conduct. The community partners were actively involved in generating ideas as well as providing feedback, comments, and criticism in an iterative process to refine the questions and improve the language and clarity of the survey, assist in recruiting, and discussing study findings.

This was embedded in a sequential, explanatory mixed-methods approach (Creswell & Plano Clark, 2011). In this design (QUANT→Qual), quantitative data are collected first and analyzed, followed by collection of qualitative data in an effort to elucidate mechanism and explanations for significant/non-significant findings identified in the quantitative data. In the present study, the initial quantitative approach (QUANT) took the form of an online needs assessment survey and subsequent patient focus groups were conducted (Qual) to explore findings in greater detail, obtain greater insight into the unmet health needs of CHH men, and generate working explanatory models.

The rationale for applying this approach is that this mixed method provide a deeper exploration of the unmet health needs of CHH men than would be possible by either method in isolation (Creswell & Plano Clark, 2011). The quantitative data are used to examine

relationships and correlates affecting health promoting behavior while the qualitative data are used to provide context and understanding to the quantitative analysis as well as generate areas for nursing sensitive interventions.

Sample Size and Power Analysis

The requisite sample size estimate was based on Cohen's statistical power analysis for correlations. This is one of the most widely used in behavioral sciences for determining sample size (Cappelleri & Darlington, 1994). Cohen posits that a medium effect size can likely be visible to the naked eye of a careful observer (J. Cohen, 1992). Thus, for this descriptive, correlational needs assessment, power calculation was performed using a medium effect size (r=0.3, explaining 9% of the variance) with a significance of 0.05 and power of 0.80 to determine that 85 subjects would be needed to have an 80% chance of detecting a difference with 95% confidence (J. Cohen, 1988).

Inclusion and Exclusion Criteria

Inclusion criteria.

- Adult males (18-70 years of age).
- Diagnosed with CHH (i.e. normosmic CHH or Kallmann Syndrome), in order to ensure the validity of CHH diagnosis report by patients, a random sample (40%) of respondents were contacted to confirm diagnosis.
- Capable of responding to a written questionnaire in English.

Exclusion criteria.

- Men with other forms of hypogonadism (i.e. Klinefelter Syndrome or adult onset hypogonadotropic hypogonadism).
- Incomplete surveys or surveys containing inconsistent or conflicting data.

Sampling for the quantitative phase

The rarity of CHH, approximately one in 4,000-10,000 (Filippi, 1986; Fromantin et al., 1973), presents a challenge in terms of recruiting adequate numbers of widely dispersed patients (Kruer & Steiner, 2008; Watson et al., 2008). To address this, the convenience sample was preferred and potential participants were identified via several recruitment measures in collaboration with patient community leaders: i) the international network of clinicians and reproductive endocrinologists in the field (COST Action BM1105, GnRH Deficiency: Elucidating the Neuroendocrine Control of Human Reproduction, based in Lausanne Switzerland at the Center Hospitalier Universitaire Vaudois), ii) the patient-related support sites (online support group: Yahoo Kallmannn syndrome support [n= 1,738 members since site launch], social networking: Facebook [approximately 400 regular visitors - personal communication N. Smith site administrator], weblogs: (Blogspot [n=300 hits/month - personal communication N. Smith site host], Wordpress [n=600 hits/month - personal communication N. Smith site host]), iii) a link for patient participation on the COST Action website (www.gnrhnetwork.eu) and, iv) a link via the clinical trials registry of the U.S. National Institutes of health (www.clinicaltrials.gov).

To overcome the dispersed nature of rare disease patients a web-based recruitment (as described above) was used combined with web-based data collection (i.e. online survey using SurveyGizmo). Previous studies have found the internet (i.e. online web-based questionnaires) a useful tool for reaching dispersed populations (Eysenbach & Wyatt, 2002). Further, given the anonymity of online information, the internet is considered useful for eliciting information that patients may not feel comfortable expressing in face-to-face encounters with healthcare providers (Bedgood, Sadurski, & Schade, 2007). The potential

sampling bias of internet surveys is of less concern in this mixed-methods approach as the goal is to target a specific cohort of patients to explore their situation in depth (Eysenbach & Wyatt, 2002).

Sampling for the qualitative phase

Subjects participating in the patient focus groups met the following criteria: adult men (18-70 years of age) diagnosed with CHH and providing written informed consent in English. Subjects were recruited among those CHH men actively participating in a patient support group meetings jointly organized by patient community leaders and members of COST Action BM1105. Meetings were publicized on the Action website (www.gnrhnetwork.eu) and by patient community leaders online.

Variables and Measures Used in the Quantitative Phase

The variables and measures selected for this study are largely driven by the HPM. To address the four specific aims, data collection include: i) demographic information, ii) established, validated instruments (Illness Perception Questionnaire-Revised [IPQR], Zung Self Rating Depression Scale [SDS]), and iii) questions developed specifically to address aspects of the HPM in the context of the Specific Aims (i.e. personal factors [sexuality and body image], past behavior [interactions with health systems] and interpersonal influences [interactions healthcare professionals]). These questions include open ended, yes/no, and multiple choice formats. Items were formulated for relevance to the HPM and were developed through iterative discussions with three expert patients who are members of COST Action BM1105 Working Group 5: Patient Advocacy. These patient community leaders are actively involved in patient support groups and lead online discussions. The patient advocates provided input, feedback, comments, and criticism in an iterative process to refine the questions and improve the language used in the questionnaire.

Specific Aim 1 : Individual characteristics and experiences.

To assess illness perceptions and depressive symptoms in men with CHH.

Rationale. Both illness perceptions and depression have been shown to have significant impact on adherence to treatment (Ciechanowski, Katon, & Russo, 2000; Kucukarslan, 2012; Lin et al., 2004). The HPM recognizes that personal factors play an important role in shaping health behavior. Several approaches were used to assess these HPM factors (individual characteristics and experiences) and deepen the interpretation of affected illness perceptions and depressive symptoms in CHH men.

SA1.1 Prior related behavior (past experiences) was examined in terms of past interactions with the healthcare system and collecting information on the age of diagnosis and initiation of treatment (Appendix 3) as some authors have suggested that this may be an important area impacting the psychosocial effects of CHH (Bouvattier et al., 2012). Additionally subjects were asked about past experiences of discrimination in healthcare systems related to CHH (Hudelson, Kolly, & Perneger, 2010).

SA1.2 Personal factors

SA1.2.1 Biologic factors include characteristics such as gender, age, developmental status (child, adolescent, or adult), health status, and physical fitness among others. These factors were evaluated by demographic information (Appendix 3, 4). The selection of demographic variable collected in this study was guided by previous work in men with Klinefelter syndrome (Herlihy et al., 2011; Turriff, Levy, & Biesecker, 2011). Klinefelter syndrome results from an additional sex chromosome (47XXY) and is the most common chromosomal aberration in men occurring in approximately 1 in 500 live births (Turriff et al., 2011). Given the paucity of literature on CHH men, the Klinefelter syndrome patient population was

considered as a suitable surrogate as these men exhibit many similar phenotypic characteristics as CHH (i.e. testosterone deficiency, incomplete or absent puberty, small testicular size, infertility) (Herlihy et al., 2011; Turriff et al., 2011). Therefore, the following items were collected and analyzed: gender, age, education level, employment status and type of work, time since diagnosis, current and past treatments, marital/relationship status, children, relationship to children (biological/adopted).

SA1.2.2 Psychological factors include self concept/self-esteem, body image, sexuality, self motivation, and perceived health status. These psychological elements were assessed by using the Illness Perception Questionnaire - Revised (IPQ-R) (Appendix 5), the Zung Self-rating Depression Scale (SDS) (Appendix 8), and several descriptive questions related to body image and sexuality (Appendix 6). Problems with body shame and embarrassment associated related to CHH have been pointed to by some authors (Au et al., 2011) and so several questions were generated in collaboration with patient community leaders and expert patients to assess this as part of the survey. Additionally expert patients noted that intimate relationships and sexuality were frequently cited topics in online forums and thus questions were included to explore these domains. The two main questionnaires IPQ-R and the SDS are presented in the next paragraphs.

- The IPQ-R: An important psychological variable within the HPM is the individual's perception of their health status. Insight into this area has been greatly facilitated by the work of Howard Leventhal who developed the Common Sense Model (CSM) of self-regulation (Leventhal, Nerenz, & Steele, 1984). The CSM provides a framework to understand how patients integrate internal/external stimuli regarding health in the form of parallel processing that includes cognitive and affective components. In other words, an illness (or symptoms of an illness) stir cognitive interpretations of the nature

of the health threat as well as emotional interpretations (i.e. fear) generating a dynamic representation of their illness. Leventhal's model, like Pender's, is founded on the belief that people are active problem solvers who make sense of their experiences and health by constructing their own representations or models. Because illness representations are subjective, they may appear irrational or incorrect to others. However, these representations are derived from core beliefs about illness and determine guide patients' coping and actions in response to illness. Briefly, the five dimensions that form an individual's illness perception include:

- Identity: the label that the individuals describe their illness and what symptoms they believe are associated with the illness.
- Cause: the individuals' beliefs about etiology and the associated factors which caused the illness.
- Consequences: the impact and negative consequences resulting from the illness.
- Timeline: the individuals' view on the course of the illness (acute, chronic, or episodic).
- Cure/Control: the extent that the individuals believe the illness is amenable to being controlled or cured.

Researchers have used the self-regulatory model for instrument development to assess illness perceptions (Weinman, Moss-Morris, & Horne, 1996). The original IPQ-R includes scales assessing each of the five dimensions and examine cognitive representations of illness and has been applied to a number of chronic illnesses (Baines & Wittkowski, 2012; Mc Sharry, Moss-Morris, & Kendrick, 2011; J. Weinman & Petrie, 1997). The instrument was subsequently revised to improve

internal consistency in the cure/control and timeline subscales (Moss-Morris, 2002). The Revised instrument - IPQ-R added several elements that have implications for coping behavior and outcomes: i) an addition of the concept of cyclicity to the timeline dimension, ii) a subscale pertaining to illness coherence to examine how individuals make sense of their illness, and iii) an emotional representation of illness providing insight into the emotional impact the illness has on a patient's life.

The revised instrument went through a rigorous validation using a cohort of over 700 patients across eight different conditions including chronic illness (asthma, diabetes, rheumatoid arthritis, chronic pain, multiple sclerosis), infectious disease, myocardial infarction, and acute pain (Moss-Morris, 2002). The internal reliability of the seven subscales were good with Crohnbach alpha's ranging from 0.79-0.89 and test-retest reliability reflected acceptable stability at both short –term (3 weeks) and long-term (6 month) retest. The discriminant ability to identify known groups (i.e. acute vs. chronic pain patients) was evaluated and all seven dimensions of the IPQ-R and were significantly different between groups.

In the 10 years since the introduction and validation of the IPQ-R, the instrument has been used to understand illness perception in chronic conditions (Baines & Wittkowski, 2012; Bijsterbosch et al., 2009; Chilcot, Wellsted, & Farrington, 2010; Fischer et al., 2010; Fowler & Baas, 2006; Mc Sharry et al., 2011; Searle, Norman, Thompson, & Vedhara, 2007), endocrine disorders such as acromegaly (Tiemensma et al., 2011a) and Cushing's syndrome (Tiemensma et al., 2011b) and to better understand issues relating to adherence to treatment (Aflakseir, 2012; J. C. Chan et al., 2009; French et al., 2008; Ohm & Aaronson, 2006). Leventhal's common sense model

of self-regulation, and the instruments derived from his work, have been useful in relation to nursing as they can be used to both guide care activities as well as demonstrate how nursing interventions positively impact measurable patient outcomes (Johnson, 1999).

In this proposed study, the IPQ-R affective illness representations dimension is utilized to examine the illness perception of CHH patients (Appendix 5). The reasons for this are two-fold. The first lies in the theoretical similarities and coherence between Leventhal's CSM and Pender's HPM. Leventhal poses that internal and external stimuli are critical elements in forming illness perceptions, which ultimately determine coping. Similarly, within Pender's individual characteristics and experiences axis of the HPM, there is strong co-linearity between external factors i.e. prior related behavior and internal stimuli i.e. personal factors including biologic, psychological, socio-cultural elements. In the HPM, these interact to create behavior-specific cognitions and affect while in the CSM, parallel processing occurs to determine coping. As such, the IPQ-R is a useful instrument in characterizing the individual characteristics and experiences axis of the HPM. Secondly, the IPQ-R is highly applicable as it has previously demonstrated utility in relation to chronic diseases, endocrine disorders, and adherence to treatment – all of which are relevant to the proposed study.

- The SDS: To assess depressive symptoms in the CHH population, the SDS will be used (appendix 8). This instrument was developed by William Zung in an effort to develop a self-report test to quantify depression severity (Zung, 1965). The instrument is a simple and rapidly administered with balanced questions (10 positively worded

and 10 negatively worded) examining common symptoms of depression. The SDS utility as a screening tool has been demonstrated (Zung, 1990) and has widely been used a measure to evaluate treatment effectiveness (Shafer, 2006). This self-report instrument scores range from 20-80 which can be translated to four levels of depression symptoms: level 0 (normal range) no significant depressive symptoms; level 1 (mild) corresponding with significant depressive symptoms yet typically below what would normally initiate a referral for treatment; level 2 (moderate) corresponding with what might typically be observed among outpatient depression patients or those with dysthymia; level 3 (severe) marked symptoms characteristic of major depressive disorder. This instrument is internally consistent with split half reliability coefficients ranging between 0.73-0.79 (Hedlund & Vieweg, 1979). Further, evidence of its construct validity comes from its relationship with other clinical depression scales (Faravelli, Albanesi, & Poli, 1986). The Zung SDS has demonstrated intercorrelations with a wide number of other widely used depression inventories including: Depression Scale inventory (0.87) (Zung, 1972), Hamilton Depression Rating Scale (0.80), Bunney and Hamburg Rating Scale (0.57) (Faravelli et al., 1986), Wechsler Depression Rating Scale (0.54) (Faravelli et al., 1986), as well as global physician ratings of clinical depression (0.69) (Biggs, Wylie, & Ziegler, 1978). One advantage of using this instrument is that it has been used widely across numerous patient and community dwelling population thus providing ample data to estimate community base rates of depressive symptoms for comparison.

SA1.2.3 Socio-cultural factors include characteristics like race, ethnicity, education level, health literacy and socioeconomic status. Previous work on health literacy has demonstrated a self-report method involving a single question corresponds with lengthier gold standard

literacy tests (Chew, Bradley, & Boyko, 2004; Chew et al., 2008). Therefore this abbreviated approach was used to assess level of healthcare literacy among survey respondents. Socio-cultural factors were assessed by evaluating independent demographic variables such as education level that can be a potentially confounding variable for data interpretation (Appendix 3, 4).

Specific Aim 2: Behavior-specific cognitions and affect.

To explore CHH patients' perceived barriers related to health promoting behavior

Rationale: Assessing perceived barriers to health promoting behavior is an initial and fundamental step in developing interventions that either remove the barriers or facilitate patients' ability and confidence to overcome them. The individual characteristics (i.e. biological, psychological, and socio-cultural elements as described above) interact with a number of elements with strong co-linear relationships.

SA2 Perceived benefits to action, Perceived barriers to action, Perceived self-efficacy, Activity related affect were explored in patient focus group discussions to gather patient-reported outcome data. Additionally, as detailed above, the IPQ-R already includes elements of personal control and treatment control which are used as additional proxy measures related to self-efficacy in terms of adherence to treatment (Appendix 5). The other areas were explored in a series of semi-structured patient focus groups. The patient focus group discussions were in-person, face-to-face and were led by the investigator. Additionally, an expert patient (community leader) also attended to help facilitate the discussion and to help the participants feel comfortable with sharing their experiences. Open ended questions (Appendix 9) were asked to probe the main thematic elements identified form the online survey and assessing aspects of the HPM. The emphasis of the focus group were to stimulate

discussion and collect both similar and discordant viewpoints that include both positive and negative commentaries to deepen inferences generated from the quantitative analysis and generate working explanatory models (Creswell & Plano Clark, 2011).

Specific Aim 3: Interpersonal influences.

To describe the type and quality of interactions with healthcare providers

Rationale: Effective provider-patient communication has long been demonstrated to positively impact health (Kaplan, Greenfield, & Ware, 1989). Conversely, poor communication can lead to patient perceptions that providers lack empathy or are dismissive of their feelings (Bodenheimer, 2005a). Further, discordance between patients and providers can negatively impact patient care, adherence to treatment and health-related outcomes (Starfield et al., 1981). Within the HPM, healthcare providers as well as friends, peers and family provide important interpersonal influences on health promoting behavior. As such these influences were examined to deepen the interpretation of adherence (SA4).

SA3.1 Interpersonal influences (healthcare providers) were examined both in the online survey as well as in patient focus groups. Aspects regarding healthcare interactions include whether or not patients have been seen at specialized academic medical centers and if they have had genetic testing/counseling. Subjects were asked about their perception of their healthcare provider's competence (i.e. medical management of CHH) and empathy (understanding how patients feel about living with CHH) and if they have ever discussed counseling with their healthcare provider or have received a referral for psychological support (Appendix 4). Focus group discussions explore interactions with healthcare providers and were analyzed to identify types of interactions that support effective coping and those which undermine patients' sense of wellbeing.

SA3.2 Interpersonal influences (friends/peers/ family) were explored in the online survey and in focus groups discussions. The online survey assessed where patients find information about CHH and what sources are deemed the most important (Appendix 4). Patient focus group discussions permitted to examine how patients deal with living with CHH with particular attention on effective coping strategies and from whom patients draw on for emotional and psychological support (Appendix 9).

Specific Aim 4: Behavioral outcome/Health promoting behavior.

To evaluate adherence to treatment in men with CHH

Rationale: Adherence to treatment is a widely-recognized and significant problem in healthcare and in particular in chronic disease as an estimated 50% are challenged to meet prescribed regimens regardless of disease, prognosis, or setting (Dunbar-Jacob et al., 2000). There is a paucity of data on adherence to treatment in CHH and the few reports examining this specific question in men living with CHH indicate that anywhere from 25-34% of patients have problems with adherence (Huffer et al., 1964; Laitinen et al., 2012a). Further, complicating this issue is the fact that there is no single agreed upon standard as to what constitutes an adequate level of adherence (Osterberg & Blaschke, 2005). The WHO (2003) defines adherence as "*the extent to which a person's behaviour - taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider*" (p. 17). For the purpose of this study, assessment of non-adherence includes activities related to taking prescribed medication and engaging with the healthcare system and the following elements were used for the operational definition of non-adherence:

- *Medication related non-adherence*: not filling prescriptions or deciding not to take prescribed medication, taking medication at different dose or frequency than prescribed, or discontinuing/stopping treatment outside of any provider recommended treatment washout (Osterberg & Blaschke, 2005).

- *Healthcare related non-adherence:* not scheduling/attending follow-up medical appointments, not having recommended diagnostic testing performed, not having monitoring tests performed (i.e. blood draws to monitor serum hormone levels and treatment effectiveness)(Vermeire, Hearnshaw, Van Royen, & Denekens, 2001).

To avoid stigmatizing non-adherence, questions relating to adherence were framed with the underlying assumption that all patients have difficulty with adherence, and separating medication adherence from healthcare adherence.

SA4 Health promoting behavior (adherence) was evaluated by assessing adherence to medication and healthcare. Patient-reported medication adherence was evaluated using the Morisky Medication Adherence Scale (MMAS) (Morisky, Ang, Krousel-Wood, & Ward, 2008). The 8-item questionnaire assesses different aspects of medication taking behavior such as forgetting to take medication, difficulty with maintaining a treatment plan, missing doses, and intentionally stopping medication. Based on these score, patients can be categorized as having low (score=1-5), medium (score=6-7), or high adherence (score=8). While not an objective measure of medication adherence, self reported measures have the advantages of being acceptable to patients, easy to use and reasonably valid (Garfield, Clifford, Eliasson, Barber, & Willson, 2011). The MMAS is a widely used, reliable self-report instrument that has shown concordance with objective pharmacy refill records (Krousel-Wood et al., 2009; Marcum, Handler, Boyce, Gellad, & Hanlon, 2010). It has demonstrated good concurrent and predictive validity with 93% sensitivity and 53% specificity among patients taking medication for hypertension (Morisky et al., 2008).

Some criticize self-report assessments of medication adherence as an inherently flawed method. An alternative approach would be to perform retrospective chart reviews and comb

pharmacy refill information, but given the internationally dispersed sample, these are beyond the scope of this needs assessment study. Further, there is no gold standard definition of what is adherence and what is an acceptable level of adherence and pharmacy refill records only indicate what prescriptions have been filled, not what medications have been taken. Therefore, this study represents a first pass to obtain general information about adherence patterns in this patient population according to patients' views. In addition to the MMAS, patients will be asked their longest duration of non-adherence (both for medication and healthcare) (Appendix 7). Aspects of will adherence are addressed in the focus group discussions.

Quantitative Data Analysis Plan

Quantitative data collected in the online survey are reported using descriptive statistics such as mean ± standard deviation, range, median). Pearson product-moment correlation coefficients will be used to examine associations between variables and survey responses (i.e. depressive symptoms, medication adherence, and selected subscales of the IPQ-R). Additionally, comparisons between groups (i.e. based on yes/no response) are made using Student's t-test or Wilcoxon rank-sum test when data are not normally distributed. Other statistical approaches include:

- Chi square: to compare the proportion of respondents who perceive their healthcare provider understand the medical aspects of CHH and the proportion of respondents who perceive their provider understands the emotional impact of CHH (Appendix 4).
- Kruskall-Wallace one-way analysis of variance: to assess the relative importance of the most frequently used sources of information on CHH (appendix 4).
- ANOVA with Bonferroni post-hoc correction for multiple comparisons: to compare scores of the IPQ-R dimensions between CHH men and reference cohorts. Because the general population does not have an illness, there are no normative data for the

IPQ-R. Therefore, several reference groups were used to provide clinical context for these data. Literature reference on values in patients with long-term remission of acromegaly were obtained (Tiemensma et al., 2011a) as well as acute and chronic pain (Moss-Morris, 2002). The reference patients with long-term remission of acromegaly included 81 patients (47 men, 34 women, mean age 60 ± 12yrs) All patients had long-term biochemical control of acromegaly with a mean duration up 16 ±10 years. Because illness perceptions assess the perceptions of a specific disease, there are self-evidently no norm values for the general population, so scores of patients with acute and chronic pain have been used instead to provide meaningful context (Moss-Morris, 2002). The reference group with acute pain consisted of 35 subjects who were recruited from a private practice for physical therapy (20 men, 15 women, mean age of 36±12yr). These patients presented with a first-time peripheral painful injury that had been present for less than six weeks. The reference group of patients with chronic pain consisted of 63 subjects (26 men and 37 women, with a mean age of 54±11yr) who were recruited from hospital-based chronic pain clinics. All patients experienced pain for longer than three months which was unexplained by medical signs alone.

- Linear regression: to assess the possible effect of age of diagnosis or duration of treatment on medication adherence.
- Z-score: to assess differences in proportions of CHH men reporting they have never been sexually active (Appendix 6) with a reference group. The CHH cohort will be compared to a large probability sample (n=2,058) of adults surveyed about sexual behavior (Leigh, Temple, & Trocki, 1993). Additionally, the same approach is used to compare the proportion of CHH men exhibiting mild, moderate and severe depressive symptoms (Appendix 8) compared to a reference group. One advantage of utilizing

the SDS is that the wide use of this validated instrument makes reference data available (Blumenthal, 1975). The reference group used for the SDS analysis was published previously by Barrett and colleagues examining community base rates for depressive symptoms (Barrett, Hurst, DiScala, & Rose, 1978). This study collected from a group of 292 community-dwelling, healthy, employed men (mean age 36 yrs, range 25-49) who underwent monthly administration of the SDS for a full year to determine prevalence rates of depressive symptoms among a non-patient, functioning population of untreated men. This published community base rate was used as the comparator for the CHH cohort.

Qualitative Data Analysis Plan

The qualitative data was collected from a series of three semi-structured focus groups involving a total of 26 CHH patients. Questions for the focus group included several open ended questions to exploring challenges of CHH and impact on quality of life, impact on intimate/sex life, coping/support, and adherence (Appendix 9). Focus group questions articulate with the 3 components of the HPM: individual characteristics and experiences (i.e. psychological profile including body image, sexuality, illness perceptions and depression – Appendix 9 questions 1 and 2), activity related cognitions and affect (i.e. interpersonal influences and support - Appendix 9 question 1), and health promoting behavior (i.e. adherence to treatment – Appendix 9, question 3). The discussions were recorded and digital audio files saved on a password protected laptop, anonymized and transcribed verbatim and uploaded into QSR NVivo™ (QSR International PTY Ltd, Melbourne, Australia) to facilitate thematic analysis (coding).

Thematic analysis was used to examine the qualitative data. A structured, multi-step process was used to analyze narrative materials in order to identify and report themes from such

qualitative data (Braun & Clarke, 2006). Through this iterative process, text data was reduced into summary categories or themes enabling the investigator to make inferences about the data (Hsieh & Shannon, 2005). First, transcripts were read several times and elements coded into nodes according to: i) respondents actual words/statements and ii) concepts derived from their responses and iii) HPM dimensions. The nodes containing words, ideas, concepts, and phrases were then organized and sorted into coherent themes and categories. Coding was conducted by two separate investigators independently (PhD candidate Dwyer and thesis advisor Morin) to generate initial codes from the HPM and to establish new codes from emerging themes. Comparisons were made on individual coding and discrepancies were discussed until agreement was met on themes and coding. This iterative process occurred until saturation, the point at which no new themes emerge and consensus is set. The least coded themes were reviewed to see if they related or could be included with more frequently coded themes and thus condensing the codebook into a tightly focused, thematic grouping of elements. Additionally, connections between coded terms were mapped to examine co-occurring themes and connections within and between categories (i.e. whether or not certain themes appear together repeatedly) (Saldana, 2009). Additionally, themes arising frequently and expansively were given a particular emphasis. Vivid and compelling quotes sere extracted as examples of the themes and themes were visually presented and mapped to conceptualize the qualitative data. This process was used to analyze patients' responses, experiences, and perspectives to elucidate explanatory mechanisms that help clarify the quantitative findings (Creswell & Plano Clark, 2011).

One criticism levied against such an approach to analysis is that pre-set categories can be a source of bias leading to an overly deterministic approach (Jackson & M., 2002). Therefore, to avoid this potential source of bias, a minimal *a priori* set of categories was established.

Coded responses were reviewed in aggregate to identify recurrent consistencies/inconsistencies from which thematic elements emerge and connections between coded terms mapped to examine co-occurring themes. Further, themes were ranked on relative importance based on the frequency of responses (Priest, Roberts, & Woods, 2002; L. Woods, Priest, & Roberts, 2002). Themes and connections were used to provide additional context and richness to the discussion of the quantitative results and help elucidate explanatory mechanisms for significant findings. This sequential explanatory mixed-methods approach was intended to provide the basis for identifying the specific nursing-sensitive targets for future web-based interventions.

Quantitative data collection procedures

Participants were given the option of completing an online or paper version that can be returned by mail. The first page included a detailed description of study aims and an explanation that some of the survey questions will be on sensitive matters and that participants are not required to responds if they are uncomfortable. However, the rationale for these questions was presented to explain that by answering these sensitive questions, participants will help better understand the healthcare needs related to CHH. Issues relating to confidentiality were explicitly stated with a description of the safeguards in place to protect confidentiality (and for online participants - an assurance that cookie tracking is off). Subjects opted in by clicking an “I agree” radio button or by completing the questionnaire and returning it by mail. Based on the SurveyGizmo algorithms and feedback received from the consulting patient community leaders, the entire process took less than 20 minutes to complete.

After completing the questions, participants were thanked for their participation and provided with contact information for an expert in the field so that they can discuss questions or

concerns that may have been raised by participating in the survey and all participants had the option to provide their information (phone or email - in a double entry format to avoid errors) to be contacted. Per ethics committee requirement, participants in the online survey are not obliged to provide contact information. Subsequently, to confirm CHH diagnosis, every other respondent providing contact information was contacted. Three attempts were made to reach the participant, and if this was unsuccessful as the participant was not able to be contacted within three attempts, then the preceding subject (then proceeding subject) was contacted to reach a 40% confirmation rate for the overall cohort included in analysis. Survey data was downloaded in Excel format statistical analysis.

Qualitative data collection procedures

Focus groups were held in concert with patient support meetings that are planned in collaboration with the patient advocates/patient community leaders. For example, the support groups meetings will be planned for the morning and participating patients will be invited in advance for an afternoon focus group discussion and provided with information sheets and consent forms to review. Potential participants can then contact the investigator with questions and decide whether or not they wish to participate. This approach was used to avoid coercion and to recruit highly motivated patients who are eager to share their concerns and experiences. All patient focus group discussions were held in the afternoon following a morning patient support meeting. Focus group sessions began with a review of the project, the nature of the focus group and the confidential nature of the discussion followed by signing of written informed consent (with subjects receiving a copy of the signed consent). The emphasis was put on fostering discussion among members relating to the open-ended questions (Appendix 9). Focus groups lasted approximately 90 minutes.

Ethical Considerations

Although this study is neither interventional nor involved genetic investigations there are still relevant ethical considerations and the full proposal was submitted to the Cantonal Ethics Commission on Health Research for review and the study began once the ethics approval was received.

It is possible that some of the participants may be depressed or have unmet healthcare needs (i.e. non-adherence or no access to a provider with expertise in CHH). Because the online survey is anonymous (it is not obligatory for patients to provide their contact information) we wanted to make sure that participants at risk are directed appropriately to seek care. To address these risks, a statement has been added to the written and a pop-up *window to the online survey stating "Your score on this survey may indicate that you have clinical depression. If you are concerned that you may be depressed we strongly encourage you to contact your physician/healthcare provider. There are treatments available for depression. Please contact the investigator with questions about this*". In this way, if patients do not provide contact information they are directed to seek medical care. Lastly, at the conclusion of the questionnaire the link for the COST Action is provided (www.gnrhnetwork.eu) with a comprehensive listing of providers with expertise in treating CHH and a listing of specialized referral centers so that patients can identify expert care in their region.

Focus groups participants provided a written informed consent prior to study participation. Some of the data collected in this study will be of a sensitive nature and as such participants will be reminded that the discussions remain confidential. For the focus groups, discussions were digitally recorded (audio) and immediately downloaded onto an encrypted, password protected laptop computer. Transcribed data were coded so it is not directly linked to

individuals. Specifically, the coding was assigned during the transcription process to anonymize patients. For example, the first participants in the first focus group would be assigned P1, P2, P3, P4, and so on. All study data was stored in a limited access, firewall protected, secure database.

Chapter IV: Results

As explained in the Preface, this chapter is composed of three original articles which present the study results. Each article has been submitted to a peer-reviewed journal. It is included in the format required by the thesis.

As a reminder, the main objective of this thesis was to examine the unmet health needs in a rare disease patient population using the nursing-sensitive Health Promotion Model (HPM) (Pender, Murdaugh, & Parsons, 2010) as a theoretical foundation. It was designed to specifically pursue four specific aims and the articles were constructed to address these.

Specific Aim 1 concerning individual characteristics and experiences.

Its objective was to assess illness perceptions and depressive symptoms in men with CHH. All three articles included elements within Pender's individual characteristics and experiences domain. More specifically, article n°2 reported illness perceptions and depressive symptoms in men with CHH. Further, article °3 reporting the psychosexual impact of CHH relates specifically to the individual characteristics and experiences domain of the HPM (i.e. psychological traits such as self esteem, body image and sexuality).

Specific Aim 2 concerning behavior-specific cognitions and affect.

Its objective was to explore CHH patients' perceived barriers related to health promoting behavior. Article n°2 specifically addressed barriers to health promoting behavior and examined self-efficacy using the IPQ-R as well focus groups discussions.

Specific Aim 3 concerning Interpersonal Influences.

Its main objective was to describe the type and quality of interactions with healthcare providers. Within the Pender's HPM, interpersonal factors are a critical modifiable element for enhancing health promoting behavior. As depicted in all three articles, the impact of interactions with healthcare professionals was described and areas for enhanced communication and shared decision-making were identified. Findings from both the online survey and patient focus group discussions revealed that online community is a critical support for these men in article n°1. This finding was explored in focus groups and points to the acceptability of online interventions and peer-to-peer support as viable avenues for meeting some of the unmet health needs in these dispersed patients.

Finally, specific Aim 4 concerned Behavioral outcome, and health promoting behavior. Its objective was to evaluate adherence to treatment in men with CHH. The HPM was here again utilized to examine CHH men's health promoting behavior in relation to adherence to treatment and healthcare. Both article n°1 and article n°2 depict that these men often struggle to adhere to their medication regime and frequently have discontinuities in care which can have major health consequences.

Article n°1

Authors, Title and Journal

Andrew A. Dwyer, Richard Quinton, Diane Morin & Nelly Pitteloud Identifying the unmet health needs of patients with congenital hypogonadotropic hypogonadism using a web-based needs assessment: Implications for online interventions and peer-to-peer support. *Orphanet Journal of Rare Diseases*. (Accepted June 4, 2014 – Appendix 10)

Affiliations of Authors

AD : University of Lausanne, Institut universitaire de formation et de recherche en soins and the Endocrinology, Diabetes & Metabolism Service of the Centre Hospitalier Universitaire Vaudois, 46 Rue du Bugnon , Lausanne 1011, Switzerland, andrew.dwyer@chuv.ch

RQ : University of Newcastle-upon-Tyne, Institute of Genetic Medicine and the Royal Victoria Infirmary, Newcastle-upon-Tyne NE1 3BZ, United Kingdom, richard.quinton@nuth.nhs.uk

DM: University of Lausanne Institut universitaire de formation et de recherche en soins, Biopole 2 - Route de la Corniche 10, Lausanne, 1010, Switzerland, diane.morin@unil.ch

NP: University of Lausanne and the Endocrinology, Diabetes & Metabolism Service of the Centre Hospitalier Universitaire Vaudois, 46 Rue du Bugnon, Lausanne, 1011, Switzerland, nelly.pitteloud@chuv.ch

Corresponding Author:

Andrew Dwyer, Endocrinology, Diabetes & Metabolism Service, Centre Hospitalier Universitaire Vaudois, Rue du Bugnon 46, BH19.317, CH-1011 Lausanne, Switzerland.

andrew.dwyer@chuv.ch

Abstract

Background

Patients with rare diseases such as congenital hypogonadotropic hypogonadism (CHH) are dispersed, often challenged to find specialized care and face other health disparities. The internet has the potential to reach a wide audience of rare disease patients and can help connect patients and specialists. Therefore, this study aimed to: (i) determine if web-based platforms could be effectively used to conduct an online needs assessment of dispersed CHH patients; (ii) identify the unmet health and informational needs of CHH patients and (iii) assess patient acceptability regarding patient-centered, web-based interventions to bridge shortfalls in care.

Methods

A sequential mixed-methods design was used: first, an online survey was conducted to evaluate health promoting behavior and identify unmet health and informational needs of CHH men. Subsequently, patient focus groups were held to explore specific patient-identified targets for care and to examine the acceptability of possible online interventions. Descriptive statistics and thematic qualitative analyses were used.

Results

105 male participants completed the online survey (mean age 37±11, range 19-66 years) representing a spectrum of patients across a broad socioeconomic range and all but one subject had adequate healthcare literacy. The survey revealed periods of non-adherence to treatment (34/93, 37%) and gaps in healthcare (36/87, 41%) exceeding one year. Patient focus groups identified lasting psychological effects related to feelings of isolation, shame and body-image concerns. Survey respondents were active internet users, nearly all had sought

CHH information online (101/105, 96%), and they rated the internet, healthcare providers, and online community as equally important CHH information sources. Focus group participants were overwhelmingly positive regarding online interventions/support with links to reach expert healthcare providers and for peer-to-peer support.

Conclusion

The web-based needs assessment was an effective way to reach dispersed CHH patients. These individuals often have long gaps in care and struggle with the psychosocial sequelae of CHH. They are highly motivated internet users seeking information and tapping into online communities and are receptive to novel web-based interventions addressing their unmet needs.

Keywords

congenital hypogonadotropic hypogonadism, Kallmann syndrome, community based participatory research, internet, e-health, rare diseases, health promotion, patient-centered care, nursing

Background

Patients affected by rare diseases are dispersed and face a variety of challenges including lack of specialized care, delays in diagnosis, negative social consequences and other psychosocial burdens. The European Organization of Rare Diseases has previously reported a variety of obstacles these patients face (EURORDIS, 2009). Many of these are critical social determinants of health that place rare disease patients in the realm of health disparities (Holtzclaw Williams, 2011). Further, beyond disease and symptom burden, the rarity of the condition can result in patients and families feeling marginalized. In addition, the psychosocial impact of perceived invisibility, isolation, and feelings of powerlessness can

have significant deleterious impact on quality of life (Cohen & Biesecker, 2101; Huyard, 2009; Nettleton et al., 2005). One way that patients and families have overcome this is by embracing technology to access information and connect with other patients online (Fox, 2011; Tozzi et al., 2013). Advances in information technology and communications are creating cultural shifts and are changing how people develop expertise. These trends have important implications for healthcare systems and particular relevance for empowering patients dealing with rare diseases(Ayme et al., 2008).

Congenital hypogonadotropic hypogonadism (CHH, ORPHA174590) is a rare, genetic, endocrine disorder which is clinically characterized by incomplete/absent puberty and infertility as a result of a deficiency of gonadotropin releasing hormone. When it occurs with an absent sense of smell it is termed Kallmann syndrome (KS, ORPHA478). While incidence is difficult to assess, it is estimated at one in 4,000-10,000 based on a study of French conscripts (Fromantin et al., 1973). Additionally, it is 2-5 times less frequent in females than in males though this gender discordance may represent a bias of ascertainment (Hu et al., 2003; Quinton et al., 2001; Seminara et al., 1998). Most cases are sporadic, consistent with a condition which impairs fertility, yet approximately a third of cases display a familial pattern of inheritance(Quinton et al., 2001; Seminara et al., 1998). CHH is clinically heterogeneous and may occur with variable reproductive (e.g. undescended testes with/without micropenis) and non-reproductive phenotypes such as including eye/ear anomalies (including sensorineural deafness, cleft lip/palate, skeletal anomalies, osteoporosis, metabolic disturbances and renal agenesis (Mitchell et al., 2011).

As with other rare disorders, CHH patients often experience delays in diagnosis. For these individuals, the absent sexual development of CHH becomes increasingly apparent as peers and younger siblings advance through puberty while they remain in a preadolescent state.

This experience can have significant emotional and psychological consequences - as depicted in an early case series (Huffer et al., 1964) and and reiterated in a recent patient account (Smith & Quinton, 2012). Indeed, studies of newly diagnosed adolescent males with CHH indicate higher levels of anxiety and depressive symptoms compared to peers (Aydogan et al., 2012b; Lasaite, Ceponis, Preiksa, & Zilaitiene, 2013). However, the long-term impact on CHH patients has not been examined. Unlike many other orphan diseases, there are effective treatments available. Hormone replacement therapy can induce development of sexual characteristics and in most cases, fertility (Pitteloud et al., 2002; Liu et al., 2009; Warne et al., 2009). Cases of spontaneous reversal has been documented (Raivio et al., 2007), yet patients typically require lifelong therapy. Importantly, normalizing the serum hormone levels does not completely ameliorate the biopsychosocial effects that CHH patients experience. A study of adolescent CHH patients indicated improved mood after 6-months of treatment, yet significant physical and emotional role difficulties persisted compared to healthy peers (Aydogan et al., 2012). These factors may impede adherence to treatment which is a widely-recognized and significant problem in healthcare, particularly in chronic disease, as an estimated 50% find it challenging to meet prescribed regimens regardless of disease, prognosis, or setting (Dunbar-Jacob et al., 2000). Patients with chronic conditions provide approximately 95% of their care (Funnell & Anderson, 2000) and thus, adherence problems can have important health ramifications. Non-adherence in men with CHH causes hormone levels plummet and patients become hypogonadal, placing them at risk for osteoporosis, anemia and metabolic problems such as insulin resistance (Brand et al., 2011; Corona, Monami, Rastrelli, Aversa, Sforza, et al., 2011; Ding et al., 2006; Finkelstein et al., 1987; Popat et al., 2009; Yialamas et al., 2007). A study examining bone health of a cohort of 26 Finnish patients indicated 35% of patients had non-adherence periods exceeding 5 years (Laitinen et al., 2010). So despite the availability of effective treatments, there are seemingly

other issues diminishing CHH patients' self-care practices. However, we do not know the extent of problems with adherence among the general population of CHH men nor do we understand patients' perceived barriers to adherence and health promoting behavior.

Therefore, the aim of this study was threefold. First, to examine the utility of web-based platforms for reaching dispersed CHH patients and conducting an online needs assessment. Second, to better define patterns of adherence to treatment and unmet health and informational needs of CHH patients. Third, to identify specific patient-reported targets for care and assess the acceptability of launching patient-centered e-health interventions to enhance self-care and health promoting behavior.

Methods

This study utilized a community based participatory research framework. This approach has previously been put forth as a useful research model for empowering patients and overcoming health inequities (N. B. Wallerstein & Duran, 2006). As part of a European network focused on CHH (COST Action BM1105), partnerships with online patient community leaders (i.e. moderators of online patient support sites) were developed to contribute to the study design, recruitment, and conduct of the study. We recognized patients as experts and these partners were actively involved in generating ideas as well as providing feedback, comments, and criticism in an iterative process to refine the questions and improve the language and clarity of the survey and focus group questions. This descriptive, multivariate correlational needs assessment study employed a sequential mixed-methods design. This approach (QUANT-Qual) started with an online survey and statistical analysis of the quantitative data (Figure 1). Subsequently, patient focus groups were conducted and discussions were analyzed using a qualitative data analysis. The intention behind employing this mixed-methods approach was

to provide a deeper exploration of the unmet health needs of CHH men than would be possible by either method in isolation.

Men were targeted for recruitment as CHH is rare and male cases are 2-5 times more common than female cases Seminara et al., 1998, Mitchell et al., 2011). Men 18-70 years of age diagnosed with CHH (Young, 2012) were included in the study. A random sampling (40% of subjects) were contacted to confirm diagnosis and those outside of the age range or who had other causes of hypogonadism were excluded from analyses. The study was publicized online via a closed/private CHH social media group (Facebook), CHH forum (chat room), a clinical trials registry (www.clinicaltrials.gov), and the COST Action website (www.gnrhnetwork.eu). Focus groups were held in concert with patient-support meetings that were planned jointly by patient community leaders and study investigators.

First, the quantitative arm included an online survey to collect demographic information and to assess healthcare literacy, health information seeking patterns, interactions with healthcare system/providers, and self-reported adherence to treatment/healthcare (supplemental materials). To assess healthcare literacy we used a self-report method previously shown to correspond with lengthier gold standard literacy tests (Chew et al., 2004; Chew et al., 2008). Descriptive statistics, Chi square and Pearson product moment coefficients of correlation were performed on survey results. To evaluate the relative importance of the most frequently used sources of CHH information we performed Kruskall-Wallace one-way analysis of variance on ranks. SigmaStat (Systat Software Inc., San Jose, California, USA) was used for statistical analyses and a $p<0.05$ was considered significant.

Second, the qualitative arm involved patient focus groups discussing issues and challenges related to living with CHH, patient-reported coping strategies and the acceptability of possible online interventions. Questions were derived from Pender's Health Promotion Model (Pender, Murdaugh, & Parsons, 2010) and developed with input from patient community leaders. Focus group transcripts were analyzed using NVivo10 (QSR International PSY Ltd., Melbourne Australia). Briefly, thematic analysis (coding) was conducted by two separate investigators (AD:DM) to identify categories of responses and themes emerging from the focus group discussions and discrepancies in coding as well as emergent categories were discussed until resolution was achieved. Iterative coding occurred until no further themes are identified, suggesting a saturation point has been reached. Additionally, connections between coded terms were mapped to examine connections within and between categories (i.e. whether or not certain themes appear together repeatedly) and those arising frequently and expansively were given particular emphasis (Saladana, 2009).

The study was approved by the University of Lausanne ethics committee and informed consent was obtained from all participants. Participants in the online survey provided an electronic, opt-in format consent while focus group members provided written consent. All participants received investigator contact information to address questions/concerns and were given the option to provide an email address if they agreed to be contacted by the investigators for follow-up clarification.

RESULTS AND DISCUSSION

Web-based platforms combined with community partnerships are effective for conducting needs assessment survey in dispersed patients

The survey was online for 7-months and received a total of 230 hits. Of these, 105 (46%) were CHH men who completed the survey and met inclusion criteria. To provide context, if one takes the incidence of CHH as 1/10,000, then recruiting 100 subjects would provide an equivalent denominator of 1 million people. Thus, the web-based recruitment was an effective way to reach this dispersed population of CHH men. The sociodemographic information of the men responding to the web-based survey is provided in Table 1. These participants varied in age from 19-66 years (mean 37±11, median 36), two thirds had received education beyond high school/vocational training (69/105, 66%) and the majority were employed (79/104, 76%) across a broad spectrum of fields (supplemental materials). From the relatively advanced age of survey respondents we suspect that younger men with CHH may be lurking online to gather information but may not yet feel emotionally secure enough to discuss issues regarding their lack of sexual development. A review of the email addresses voluntarily provided by participants included email service providers from North and South America, Europe, and Australasia underscoring the global reach of online recruiting via social media for rapidly reaching dispersed patients.

Studying orphan diseases presents a challenge in terms of recruiting adequate numbers of widely dispersed patients (Kruer & Steiner, 2008; Watson et al., 2008). Previously, online web-based questionnaires have proven a useful tool for reaching dispersed populations (Eysenbach & Wyatt, 2002) and advertising on social media platforms can enhance patient recruitment efforts (Close et al., 2013, Ramo & Prochaska, 2012). Instead of using online advertising, herein we developed partnerships with online patient community leaders to reach dispersed rare disease patients and utilized web-based platforms for both recruitment and data collection. This was an effective way to reach a large audience and conduct an online CHH needs assessment. Further, such patient community partnerships may provide multiple bi-

directional benefits including connecting patients with expert care and enhancing recruitment for research/clinical trials.

CHH patients have long gaps in care

Nearly all the men (99/105, 94%) in the online survey responded that they had received testosterone therapy for CHH. Six men reported never having received testosterone; three men stated they had never been on treatment (2/3 had been recently diagnosed) and the other 3 men had only received gonadotropin injections. In total, only 24/93 (26%) of men reported never having a lapse or gap in treatment (Figure 2). However, 37% (34/93) reported having been off treatment for more than a year. Survey respondents reported similar the periods when asked about the longest duration without healthcare (supplemental materials). No correlation was observed between medication/healthcare adherence and either age of diagnosis or lifetime duration of treatment. Importantly, these gaps in treatment and care can have major health impacts on patients. Hypogonadism causes decreased libido, impaired sexual function and anemia and can have profound effects on bone density placing patients at increased risk for osteoporosis and fracture (Finkelstein et al., 1987; Laitinen et al., 2012). Further, several meta-analyses point to an association between low serum testosterone levels and the metabolic syndrome and diabetes (Ding et al., 2006; Corona et al., 2011; Brand et al., 2011). Even acute withdrawal of treatment in these men induces increased fasting insulin levels and insulin resistance within two weeks (Yialamas et al., 2007) while long-term hypogonadism carries heightened prevalence of hyperinsulinemia, metabolic syndrome and diabetes (Shahani et al., 2008). Thus, lack of or inadequate androgen replacement may heighten further health risks for CHH men such as cardiovascular morbidity. Accordingly, these represent meaningful targets for interventions to enhance adherence to treatment and self-management.

CHH patients have unmet psychosocial health needs

The online survey included several questions that were developed to examine past interactions with healthcare systems (supplemental materials) including experiences with discrimination related to their condition (Hudelson, Kolly, & Perneger, 2010). Fewer than one in five (16/105, 15%) of men reported that they had faced this type of discrimination. Notably, approximately half of the respondents (54/105, 51%) had been seen at a specialized/academic medical center. As healthcare providers exert important interpersonal influences on health promoting behavior, we queried patients about their experiences with healthcare professionals. In total, 70/105 (67%) stated that their healthcare provider understood the medical aspects of their condition. However, significantly fewer (39/104, 38%, $p<0.001$) perceived that their provider understood the emotional impact of CHH. Having a provider who comprehended the medical aspects of CHH correlated positively with being seen at a specialized center ($R=0.40$, $p<0.001$) while having a provider who understood patients' feelings about having CHH was positively correlated with having been referred for psychological counseling ($R=0.22$, $p<0.05$). The patient perspectives identified in the survey suggest that while many CHH patients are able to find and obtain specialized care/consultation with expertise in handling the medical aspects of their care, the emotional and psychological aspects of CHH are underappreciated.

Based on the survey findings we conducted three patient focus groups (n=26 total participants, mean age 37±13, range 18-66, median 36 years) to explore the challenges patients face in living with CHH and identify facilitators of adaptive coping strategies that could be leveraged for potential online interventions. What emerged from these discussions were consistent, pervasive psychological and emotional issues related to feelings of isolation and shame (Figure 3). The mean age at diagnosis was 18±5 years (range 10-27, median 17

years) and spending teenage years and young adulthood in a prepubertal body was emotionally traumatic for many. Indeed, many patients commented on their frustration with what they perceived to be a late diagnosis or a delay in initiating treatment as well as significant concerns related to underdeveloped genitalia. These experiences were linked to 4 coherent themes: i) body image concerns, ii) low self-esteem, iii) anxiety/depression, and iv) a sense of being left-behind as their peers developed into adult bodies (and adult roles) (Figure 3, Table 2). These themes were frequent and their co-occurrence within and across groups suggest that a saturation point had been reached. Thus, these unmet psychosocial health needs indicate the need for psychological support and represent targets for much-needed intervention. Notably, differences were observed across different national health systems. For instance, patients with nationalized health systems reported better continuity in care (i.e. better transitions) and fewer gaps when changing healthcare providers. In contrast, patients in individual payer systems reported significant transition problems as well as medication coverage issues both of which undermined adherence to treatment.

CHH patients have unmet health information needs

During focus group discussions, participants indicated that healthcare providers (physicians, nurses and pharmacists) played both positive and negative roles in helping them adapt to living with CHH (Table 2). Providers who were not forthcoming with information about CHH, disregarded patient concerns/feelings, did not set appropriate expectations for treatment outcomes, and did not engage patients in decisions, were sources of frustration for patients and undermined patients' sense of wellbeing. Healthcare professionals could also be powerful promoters of adaptive coping. Patients reported feeling supported by providers who expressed empathy, facilitated self-management techniques (i.e. self-injecting medications) and involved them in decision making. As such, efforts to promote patient participation in

treatment decisions and providing patient information and anticipatory guidance in lay language appear to be avenues for meeting patients' informational needs, and potentially improving patient satisfaction with care and adherence.

CHH patients rely on the internet for CHH information and peer-to-peer support

The survey participants were active users of the internet for issues related to their condition. Nearly all participants (101/105, 96%) stated they had sought information from online sources (i.e. Wikipedia). This may be related to the fact that the manifestations of CHH (sexual immaturity and infertility) are very private and personal matters and thus may contribute the high rate of anonymous information seeking that the internet provides. Less than half of survey respondents (49/105, 47%) used the medical literature as a resource for finding out about CHH. This was interesting as these men have relatively high levels of education (Table 1), yet preferred to seek information from other online resources, paralleling the increase in such practices among physicians (Kritz et al., 2013). Because the number of years of formal education may not be the best predictor of facility with medical information, we also used a previously validated self-report question "How confident are you filling out medical forms by yourself?" to screen those participants with inadequate healthcare literacy (Chew et al., 2004; chew et al., 2008). By this standard, all but one of participants had adequate healthcare literacy. Therefore, despite adequate education, appropriate healthcare literacy and access to the literature (i.e. PubMed Central), it seems that patients are much more likely to seek out information from online sources that are not part of the medical literature. Therefore, providing expert-reviewed information in lay language online could be an effective way to disseminate CHH-related health information to these dispersed patients.

The survey also revealed that patients seek information from healthcare providers and the online community in equal proportions (74/105, 70% and 81/105, 77% respectively). Further, when asked to rate the importance of healthcare professionals, online community and the internet as sources for information, all rated similarly (p=0.58). These data support the notion that for CHH patients, information from healthcare providers and members of the online community who share their condition are equally important and complementary. The importance of connecting with other patients via the online community was echoed in the patient focus groups. Participants stated that connecting with other patients online and finding out they were not alone was an important aspect of coming to terms with CHH, finding meaning in their condition, and being able to not let CHH dominate their life. Further, face-to-face encounters with other patients were often regarded as a pivotal and life-changing event (Table 3).

The data from the present study are in line with the findings of a 2011 report from the Pew Foundation that identified patients with rare diseases as the most likely group to draw upon online peer support network, even more so than those with other, more common chronic health conditions (Fox, 2011). Patient knowledge is different from that of professional healthcare providers. Patient expertise grows from a personal day-to-day experience of living with a condition and as such, patients can provide critical informational support for coping and managing one's health (Hartzler & Pratt, 2011). These complementary realms of expertise present an opportunity for collaborative efforts for health promotion and improving quality of life for patients dealing with chronic conditions (Lorig et al., 2013; Archambault, 2011, Gepta et al., 2011). Connecting with other patients is critical for CHH because it can diminish the isolation of living with a rare condition. Further, such peer-to-peer support may hold important promise for very practical and concrete benefits such as promoting adherence

to treatment and continuity with healthcare and encouraging peers to seek mental health services when needed.

CHH patients are receptive to online interventions

Focus group participants were unanimously open to and in support of utilizing online approaches to help develop coping and self-management skills. The only concern raised regarding this was the issue of confidentiality that perhaps is not surprising given the very private nature of the sexual immaturity and infertility of CHH. This mixed-methods study identified a variety of unmet health needs of CHH men. Importantly, the focus groups revealed positive examples of patients overcoming challenges, finding meaning in their condition and becoming empowered, activated patients (Table 3). As these men are active internet users and receptive to the idea of online interventions, we propose several patient-centered approaches for health promotion in these dispersed patients.

Developing online interventions to address the needs of CHH patients

Interventions addressing the identified shortfalls in care for CHH patients are intended to enhance wellness and improve coping and quality of life for these individuals. This is the fundamental objective of health promotion – the process of enabling people to overcome health challenges and increase control over their situation to achieve greater health (World Health Organization (WHO), 1986). Indeed, the Health Promotion Model (Pender, Murdaugh, & Parsons, 2010) has been used as a model to develop patient-centered approaches to activate and empower patients for self-management (Ho, Berggren, & Dahlborg-Lyckhage, 2010) and thus seems fit the needs of CHH patients. This approach acknowledges patient expertise and dramatically reframes patient involvement as well as the

role of the healthcare professionals to redefine successful health outcomes (Greenhalgh, 2009). Herein we identify three main targets for health promoting interventions (Table 2, 3).

First, CHH patients have unmet informational needs related to their condition. Given their active internet use, it seems logical to launch web-based information resources for patients and providers alike. For patients, this could include information in lay language about CHH, treatment options, and anticipatory guidance related to treatment (i.e. what to expect from treatment and in what timeframe). Further, we propose to develop materials (i.e. fact sheet of discussion points) for healthcare professionals, written by expert clinicians and available online for patients to use in order to initiate discussions with their healthcare provider on the psychological and emotional aspects of the condition and to promote shared decision-making. These materials would help contribute to create a virtual online empowerment toolkit for patients to learn about their condition, find expert care, and become empowered to take control of their health. Further, these resources could be provided in multiple languages via the European network studying GnRH deficiency (www.gnrhnetwork.eu) encompassing patient information in lay language, listings of specialized referral centers, genetic testing resources, clinical trial listings, and web-based platforms for contacting expert clinicians as well as links with peer-to-peer support.

Second, enhancing online peer-to-peer support to diminish the sense of isolation, share coping strategies and encourage peers to seek mental health services when needed to address issues of anxiety/depression. The synergy of online connectivity and patient expertise facilitates crowdsourcing for the rare disease community. Crowdsourcing is the process of tapping into the collective knowledge and problem solving abilities of a group (such as patients with a shared medical condition) to generate ideas and solutions (Howe, 2006). Importantly, online

patient communities are not intended to replace existing healthcare infrastructures, rather their expertise differs from healthcare professionals and can be valuable for peer-to-peer support and learning how to deal with issues on a daily basis (Hartzler & Pratt, 2011). Further, this pool of knowledge/experience not only impacts health management, but is also beginning to change approaches to research (Swan, 2012).

Third, to help patients address their feelings of shame, body image concerns and low self-esteem there is an opportunity to utilize online cognitive-behavioral interventions. Indeed, online education combined with peer-to-peer coaching has been successful in enhancing self-management and adherence to treatment for bipolar disorder and diabetes (Proudfoot et al., 2012; van der Wulp et al., 2012). A similar approach combining online patient education, cognitive behavioral interventions, and peer coaching could be adapted to address the specific body-image and self-esteem issues related to CHH. Further, technology may enable contact with otherwise difficult to reach patients and potentially surmount barriers that exist for face-to-face mental health treatment.

Limitations

Like other studies of this kind, this needs assessment has limitations. First, the inferences drawn from the survey findings could be strengthened by a larger sample size. Indeed, recruiting adequate numbers of rare disease patients can pose a challenge. This is why we utilized a web-based approach, yet this is not without bias as not everyone has internet access and is perhaps reflected in the fact that respondents were highly educated. Further, an online survey in English may introduce a potential Anglophone bias. Importantly, the longstanding critique of online research (access) is beginning to fade as the number of individuals lacking internet access rapidly shrinks. As of 2011, 73% of European Union households had internet

access (2/3 of which have broadband). Further, more than half of Europeans use the internet daily and just one quarter (24%) have never used the internet (Seybert, 2011) and many developing countries have "leapfrogged" straight into mobile handsets for multimodal communication and connectivity (Napoli, 2013).

Second, there are potential biases in the sampling of subjects. Participants were recruited via expert clinicians as well as among patient support groups. As medical record review was not part of this study, we recontacted 40% of respondents to confirm diagnosis. As such, we cannot be sure that every respondent met all hormonal and clinical criteria of a CHH diagnosis. However, the fact that the findings of the survey were mirrored in the focus groups (where all participants had confirmed CHH diagnosis) contributes to the validity of the study. Additionally, engaging patients in the study development and conducting an internet survey introduces sources of potential bias as these patients are the ones who seek out forums and web-based support. Similarly, those participating in patient support groups could represent men who are struggling most to deal with their condition and thus may overestimate the difficulties experienced by men with CHH. However, these issues may be less of a concern for such a needs assessment as the intent was precisely to identify a specific cohort of patients to explore their situation and perspectives in depth. While not a random sampling of patients, targeting internet users was necessary to assess the acceptability of delivering web-based interventions to patients who use the internet as a resource for health information and support. In addition, the anonymity of online information can be an asset for eliciting information that patients may not feel comfortable expressing in face-to-face encounters with healthcare providers (Bedgood, Sadurski, & Schade, 2007).

Third, the evaluation of adherence is often debated as there is no gold standard definition, no clear consensus on what is an acceptable level of adherence and self-report is subjective and an inherently flawed method. An alternative approach would be to perform retrospective chart reviews and comb pharmacy refill information, but these are beyond the scope of this needs assessment study. Rather, this survey was intended to capture a global picture adherence patterns in this patient population. The rationale for using a self-report measure was based on the fact that CHH is a chronic condition and as such, patients are responsible for the bulk of their care. Therefore, understanding patient perceptions and perspectives is a critical first step in developing patient-centered approaches to activate individuals and enhance self-management of their chronic condition.

CONCLUSIONS

Patients with CHH often have long gaps in care and struggle with significant psychosocial sequelae that are often unrecognized by the healthcare community. These patients are active internet users who draw on social media and online communities for support and to complement the information received from healthcare professionals. Patients are receptive to online interventions aimed at addressing their unmet needs. Peer-to-peer support can help enhance coping and patients should be encouraged to utilize these online communities. Drawing upon patient expertise and developing partnerships with online patient communities may provide new opportunities for health promotion and improved quality of life for these patients.

List of Abbreviations

CHH: congenital hypogonadotropic hypogonadism, KS: Kallmann syndrome, COST: European Cooperation in Science and Technology

Competing Interests

The authors have no financial or non-financial competing interests to declare.

Author's Contributions

AD conceived the study and participated in study design, conduct, analyses and drafted the manuscript. RQ participated in the coordination and conduct of the study. NP participated in study design and analysis. DM participated in study design, and analysis. All authors read and approved the final manuscript.

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Illustrations and Figures

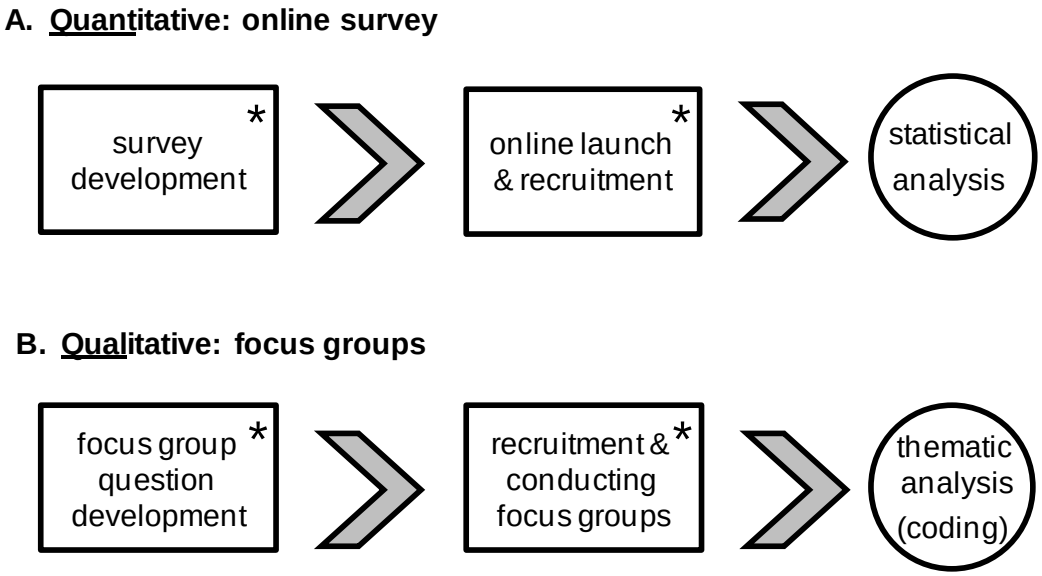

Figure 1. Study schema

Figure Legend:

Schematic depicting the sequential explanatory mixed-methods design. (A) First, a quantitative online survey was conducted and statistical analysis performed. (B) Subsequently, qualitative focus groups were conducted to explore the survey findings in detail and identify potential explanatory mechanisms. Asterisks note study stages involving participation of patient community leaders.

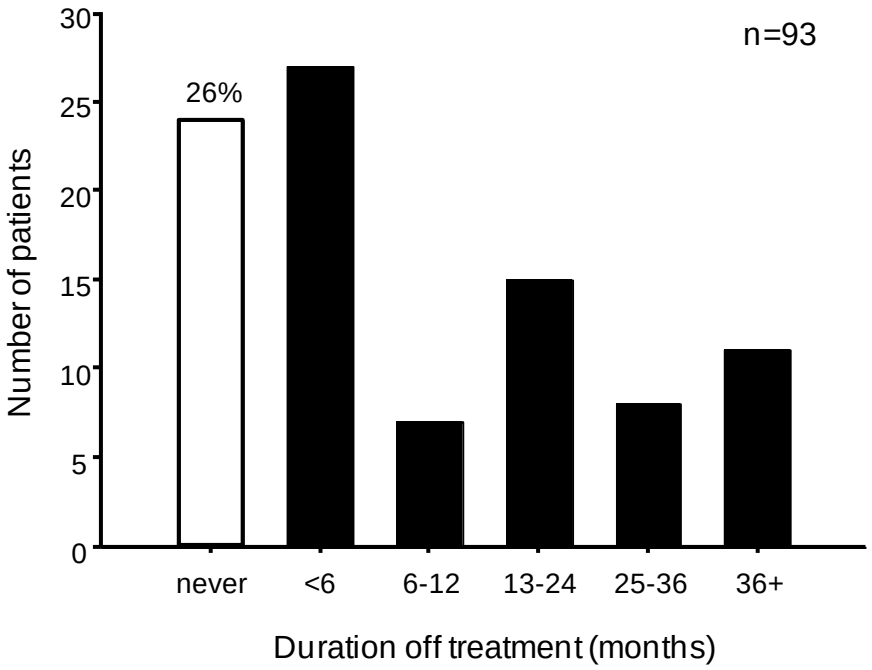

Figure 2. Adherence to treatment among CHH men

Figure Legend: Patient-reported longest duration off treatment (n=93). All men had been on treatment for at least 12 months. Only 26% (24/93) of men reported never having a gap in treatment (white bar). In total, 37% (34/93) had a lapse in treatment of more than1 year.

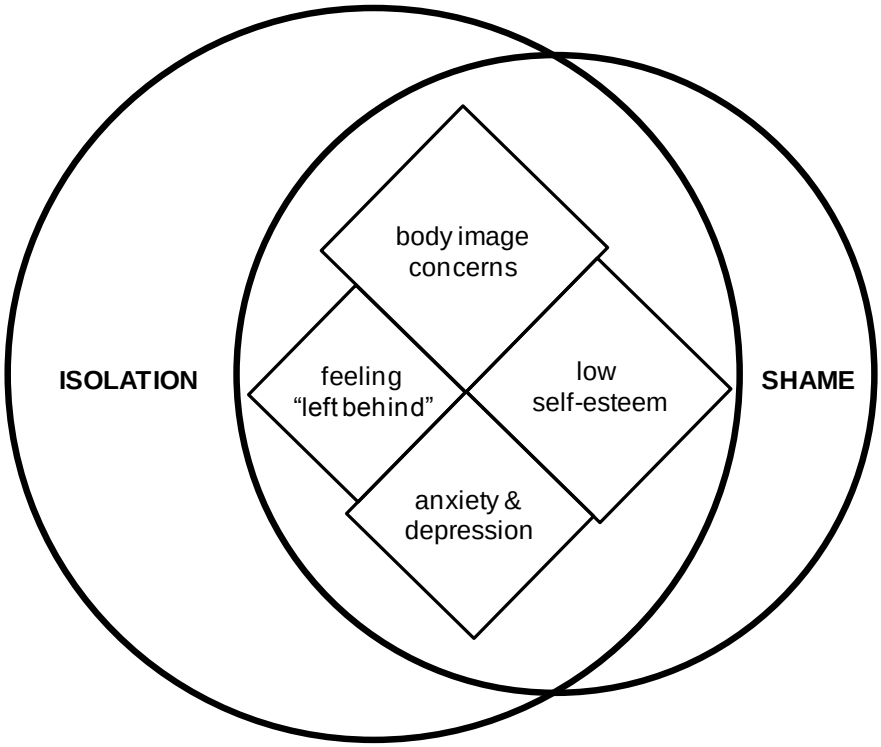

Figure 3. Patient-reported challenges of CHH

Figure Legend: Patient-reported challenges represent targets for interventions. Focus group discussions revealed two dominant themes relating to feelings of isolation and shame (depicted by circles). These themes encompassed 4 consistent, inter-related psychosocial challenges related to CHH low self-esteem, body image concerns, feeling left behind by their lack of sexual development, and issues related to anxiety and depression (depicted by diamonds). The shapes are sized according to the frequency of patient comments and overlaps and connected shapes identify co-occurring themes.

Tables and Captions

Table 1.
Sociodemographics of the CHH men completing the online survey (n=105)

Age (n=105)	**n (%)**
19-29	32 (30%)
30-39	39 (37%)
40-49	19 (18%)
50-59	11 (10%)
60+	4 (4%)
Education (n=105)	
High school/vocational	36 (34%)
University	38 (36%)
Post-Graduate	31 (30%)
Employment (n=104)	
Working full-time	70 (67%)
Working part-time	9 (9%)
Unemployed	10 (10%)
Retired	6 (6%)
Student	9 (9%)
Relationship Status (n=104)	
Married	38 (36%)
In a relationship	16 (15%)
Single	25 (24%)
Never been in a relationship	24 (23%)
Divorced	1 (1%)

Table 2.

Table of themes emerging from focus group discussions, representative quotes, and targets for interventions

Table Legend: The first column identifies thematic elements from the focus groups discussions across 2 topic areas (shaded in gray): patient-reported challenges and negative healthcare interactions. The middle column presents representative quotes for the emergent themes. The third column lists the related targets for interventions to address the unmet health and informational needs of the CHH men.

Theme	Representative quotes	Targets for interventions
Patient-Reported Challenges		
Isolation	• "I was on the outside of any social group or gathering and on the inside, I was very alone and depressed and isolated and very frightened" • "I realized that something was "wrong" with me, and didn't know what, and it looked like nobody knew. I more or less expected to have a unique disease which would have my name." • "I've pretty much been in exile for the past ten years"	Connecting with others & online peer-to-peer support
Shame		Cognitive-behavioral interventions
i. body image	• (the hardest part of CHH) "The body image problems really... I will have that until the day I die" • "I can't get undressed... I haven't been swimming in many years. I can't even pull my sleeves up... I can't sit there like you with your sleeves rolled up...I've got to keep covered."	
ii. ↓ self-esteem	• "I have a tough time engaging with people, talking with people. Usually, when I am out in public I tend to look down at the ground, because you know... I feel so ashamed" • "I always thought there was a big spotlight on me all the time. Just... self-conscious... absolutely. I got a lot of bullying and being pushed around and abused when I was young"	
iii. left behind	• "I'm 40 years old and should be at the prime of my career and I don't see myself…I don't know, it's a psychological barrier that I can't progress, I'm stuck " • "For Kallmann's (CHH), it's sort of a crucial sort of time you know, we say the psychological and emotional things are equally as big as the medical forms of treatment for it. That big, big thing (absent puberty) carries on for the rest of your life"	
iv. depression & anxiety	• "I have depression, definitely. I have noticed a common denominator with depression and self medication... myself included" • "…and my family, they weren't supportive. They didn't help me. So, I got depressed and I tried to take my own life and then um…I left to seek help on my own"	

* Quotes referencing the term "Kallmann's" refers to Kallmann syndrome - the association of CHH with the inability to smell (anosmia)

(Table 2 continued)

Negative Healthcare Interactions		
lack of information	• "The professor (doctor) who diagnosed my condition didn't even touch on the psychological side of things" • ""For the first few years after it (CHH) was mentioned to me, there was nothing at all coming back from the doctors. They didn't really tell me what I was being treated for. So it was kind of…they diagnosed me but didn't tell me and anything" • "The doctors weren't… it was just nothing. There was no real after-care at all after the diagnosis. It was just 'you need to take these injections' and that was that…you know, for the rest of your life. There was no kind of…nothing. It was a lack of communication really"	online information & resources
disregard for feelings	• "I felt like I wasn't considered intelligent enough to understand what I was being treated for. It was like 'oh, you won't understand, it's complicated'. That's it…yeah, it's not nice to be made to feel that way." • "Somebody once said something to me, actually it was an endocrinologist, and I said 'but I'm not normal' you know? And this was several years ago, and I think he was trying to say 'look, everything will be alright, keep taking your medication and all the rest of it' and I said 'I don't know what normal is'...and that didn't seem to faze him at all. I sat here saying to this professional , educated, intelligent man - he's a professor - and I was saying 'I don't know what normal is' and he didn't respond. Nothing…he didn't even look at me." • "There's no sense from anyone... about them trying to understand or even that it crosses their mind that you are going through anything. You know, that it's painful. They are just 'Mr. fix-it' - give you a prescription and you are gone"	promoting patient-centered approaches & developing a "talking sheet" to initiate discussions with providers
lack of shared decision-making	• "He (doctor) didn't give me any treatment options. He just said 'take this gel'. We didn't discuss what was the best treatment. I don't know if it was just the physician that I went to…maybe there are better ones out there who would have given me the option(s)". • "The first doctor I saw he said just take these and you'll be ok"	
discordant expectations for treatment outcome	• "No one really explained to me…I thought that if I took the testosterone…I didn't understand that…I thought that if I just took the testosterone that I would go through puberty and I would be normal." • "I said no, I can't smell a thing adn he said, 'Ah, you've got Kallmann's (CHH)!' I thought wow that's great, give me the injections and I can smell the roses and all that and well of course it didn't happen. My sense of smell never came."	online anticipatory guidance information

* Quotes referencing the term "Kallmann's" refers to Kallmann syndrome - the association of CHH with the inability to smell (anosmia)

Table 3.
Patient reported facilitators of coping

Table Legend: The first column identifies thematic elements from the focus groups discussions across 2 topic areas (shaded in gray): patient-reported challenges and negative healthcare interactions. The middle column presents representative quotes for the emergent themes. The third column lists the related targets for interventions to address the unmet health and informational needs of the CHH men.

Theme	Representative quotes	Targets for interventions
Meeting others & online support	• "Though I have a loving family I had spent most of my life feeling depressed, confused, lonely, alone, isolated, and frequently in despair. In just a couple of hours at the meeting 3 years ago... those feelings decreased. For the first time ever I was with a group of people with whom I felt normal and at ease, valued and respected. This has made a tremendous difference in my life." • "It wasn't until I found other people like (patient community leader) that I kind of filled in the blanks a bit. It was quite isolating for me and I had no one to talk to and I felt like I was the only person in the world to have this problem" • "I've really felt alone. So I went online, on Facebook just to see if there was something or a meeting and I found this group and it was the best thing I ever did because I found out there are other people and I thought I was alone. But I found others... which is really good" • "Going to my first Kallmann (CHH) meeting about 6 years ago… and until then, I was totally in the dark. And when I met up with fellow patients, I realized I'm not on my own"	Online peer-to-peer support
Coming to terms with CHH	• "Get over it, take matters into your own hands… you will get help. All you have to do is ask for it. (To the moderator) in your research, you are searching for ways that would help me… a toolkit, a fact sheet 'living with Kallmann (CHH)' that kind of thing…it also involves emotional things. If you can give that to a doctor so then that is the trigger to start a conversation. Then you can take matters into your own hands". • "So it was a change in mentality, being taunted as a child then I realized that I had to do certain things to get my life back" • "It was just the things that I would have to find out about myself that no one could tell me... and like I said, (patient community leader) has helped… Both on a personal level and for the research into the condition itself. But, being able to live with it is a very personal thing that I think you need to find out for yourself…and I think I'm coming along pretty nicely... I'm not letting it rule my life quite so much as I used to."	Patient empowerment
Positive Healthcare interactions	• "All the medical professionals I have been working with…I've been very lucky because they have always been very helpful and considerate about it. So, I guess I have been fortunate that way" • "Definitely, self-injecting (helped). Learning about the syndrome made me feel that Kallmann (CHH) is not such a big deal. But in my case, it was not enough... and the psychotherapy aspect helped a lot" • "I first heard about Kallmann's (CHH) at 25 when I moved in a new city and changed endocrinologists. That made a huge difference, suddenly she made it sounds like it was not such a big deal. In my experience female doctors are more easy to talk with, tend to ask more about how it works in the everyday life, and involve us in our prescriptions"	promoting patient-centered approaches & developing a "talking sheet" to initiate discussions with providers

* Quotes referencing the term "Kallmann's" refers to Kallmann syndrome - the association of CHH with the inability to smell (anosmia)

Additional Files: A1

A1 - Supplemental materials.

Identifying the unmet health needs of patients with congenital hypogonadotropic hypogonadism using a web-based needs assessment: Implications for online interventions and peer-to-peer support

1.Summary of online survey results

1A. Sociodemographic information
Age: [open ended response]
19-29 yrs: 32/105 (30%)
30-39 yrs: 39/105 (37%)
40-49 yrs: 19/105 (18%)
50-59 yrs: 11/105 (10%)
60+ yrs: 4/105 (4%)

Relationship status: [multiple choice]
Never been in a relationship: 24/104 (23%)
Single: 25/104 (24%)
In a relationship: 16/104 (15%)
Married: 38/104 (36%)
Divorced: 1/104 (1%)

Religion: [open-ended question]
Christian (protestant & evangelical): 25/90 (28%)
Roman Catholicism: 17/90 (19%)
Orthodox Christianity: 3/90 (3%)
(Eastern & Russian)
Islam: 5/90 (6%)
Judaism: 2/90 (2%)
Buddhism: 1/90 (1%)
Hinduism: 1/90 (1%)
Other: 10/90 (11%)
(Paganism, Mormonism, Jehovah's Witness, secular humanist, personal faith)
Atheism: 10/90 (11%)
None: 16/90 (18%)

Highest level of education: [multiple choice]
Elementary: 0/105 (0%)
High school/vocational: 36/105 (34%)
University: 38/105 (36%)
Post-graduate: 31/105 (30%)

Employment: [multiple choice]

Student: 9/104 (9%)
Working part-time: 9/104 (9%)
Working full-time: 70/104 (67%)
Retired: 6/104 (6%)
Unemployed: 10/104 (10%)

Type of employment: [open ended question - responses included]

Business & Finance
Business analyst/consultant
Economist
Finance

Law & Legal Services
Attorney
Legal assistant
Legislative consultant

Healthcare & Science
Dentist
Physician
Nurse
Pharmacist
Ambulance staff
Patient care assistant
Translation services
Biomedical scientist
Chemist/Lab Technician
Hospital finance/administration

Service & retail
Clerk
Sales/Retail
Personal trainer
Call center/customer services

Laborer & Manufacturing
Construction
Lawn care
Airline baggage
Warehouse
Milling machine operator
Quality control technician

Civil Service
civil servant
Postal worker
Juvenile services

Religious clergy
clergy

Teaching & Education
Teacher
Professor
School administrator

Psychology & social Work
School Counselor
Counselor/mediator

Engineering & Information Technology (IT)
Engineer
Electrical Engineer
Applications engineer
Network Engineer
Computer systems management
Software developer
Computer programming
IT technician

Management & supervisors
Manager - small business
Manager – manufacturing
warehouse supervisor
Purchasing manager

Transportation
Public transportation driver
Limousine Service
Truck driver

Arts & Entertainment
Composer
Performing arts
Graphic design

Buddhist monk

1B. Healthcare literacy
How confident are you filling out medical forms by yourself?
Extremely: 45/105 (43%)
Quite a bit: 34/105 (32%)
Somewhat: 25/105 (24%)
A little bit: 1/105 (1%)
Not at all: 0/105 (0%)

1C. Health information seeking patterns:
Where have you searched for information to learn about CHH? (check all that apply)
Internet (i.e. Wikipedia): 101/105 (96%)
Online community (social media/chat): 81/105 (77%)
Healthcare professionals: 74/105 (70%)
Medical literature: 49/105 (47%)
Family/friends: 12/105 (11%)
Other: 0/105 (0%)

From your experience, please rank the 3 most important sources:
Healthcare professionals: weighted score 166
Internet (i.e.Widkipedia): weighted score 150
Online community (social media/chat): weighted score 146
Medical literature: weighted score 93
Family/friends: weighted score 18

1D. Interactions with healthcare system/providers
Within the healthcare system, have you ever experienced discrimination because of CHH?
No: 89/105 (85%)
Yes: 16/105 (15%)

Have you ever had a consultation or received treatment at an academic health center (such as a teaching hospital or research center)?
No: 51/105 (49%)
Yes: 54/105 (51%)

Is there a healthcare provider (i.e. doctor or nurse) who you feel really understands the medical aspects of your CHH?
No: 35/105 (33%)
Yes: 70/105 (67%)

Is there a healthcare provider (i.e. doctor or nurse) who you feel understands your feelings about having CHH?
No: 65/104 (62.5%)
Yes: 39/104 (37.5%)

Has a healthcare provider (either general practitioner or specialist) ever offered you counseling or a referral for professional counseling?

No: 79/105 (75%)
Yes: 26/105 (25%)

1E. Diagnosis, treatment & adherence

At what age were you diagnosed with CHH? [open ended question]

Mean±SD: 18±6 years
Range: neonatal – 32 years
Median: 18 years

Lifetime duration of treatment [calculated from start of treatment]

Mean±SD: 18±12 years
Range: 0 – 46 years
Median: 16 years

What treatments have you had for CHH? (check all that apply)

Testosterone (injections, pellets, patches, or gel): 99/105
Gonadotropin/fertility injections: 37/105
None: 3/105 (two recently diagnosed patients)

What is the longest period of time that you have gone without medical care (not under the care of a doctor or healthcare provider for your CHH): [open-ended]

Never: 24/93 (26%)
<6 months: 27/93 (29%)
6-12 months: 7/93 (8%)
13-24 months: 15/93 (16%)
25-36 months: 8/93 (9%)
36+ months: 12/93 (12%)

What is the longest period of time that you have been off your CHH medication (not at the instruction of your doctor or healthcare provider): [open-ended]

Never: 28/87 (32%)
<6 months: 20/87 (23%)
6-12 months: 3/87 (3%)
13-24 months: 17/87 (20%)
25-36 months: 6/87 (7%)
36+ months: 13/87 (15%)

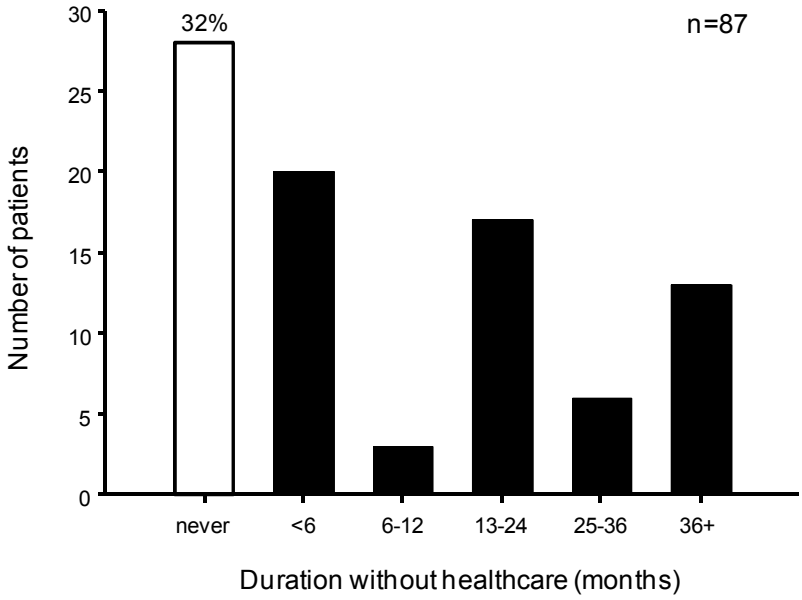

Figure S1. Patient-reported longest duration without healthcare among CHH men.

Figure Legend: Healthcare continuity as assessed by patient-reported longest period without contact with a healthcare professional (n=87). In total, 32% of CHH men reported never having a break in their continuity of healthcare while 41% had gaps in care exceeding 1 year.

Article n°2

Authors, Title and Journal

Andrew A. Dwyer, Jitske Tiemensma, Richard Quinton, Nelly Pitteloud, & Diane Morin

Adherence to treatment, depressive symptoms and affective illness representations in men with congenital hypogonadotropic hypogonadism. *Journal of Clinical Endocrinology and Metabolism* (Submitted April 12, 2014 - Confirmation of submission Appendix 11)

Affiliations

AD : Endocrinology, Diabetes & Metabolism Service of the Centre Hospitalier Universitaire Vaudois, 46 Rue du Bugnon, Lausanne 1011, Switzerland ; University of Lausanne, Institut universitaire de formation et de recherche en soins, Biopole 2, Route de la Corniche 10, Lausanne, 1010, Switzerland

RQ: University of Newcastle-upon-Tyne, Institute of Genetic Medicine and the Royal Victoria Infirmary, Newcastle-upon-Tyne NE1 3BZ, United Kingdom.

NP: Endocrinology, Diabetes & Metabolism Service of the Centre Hospitalier Universitaire Vaudois, 46 Rue du Bugnon, Lausanne 1011, Switzerland ; University of Lausanne Faculty of Biology & Medicine, Department of Physiology Rue du Bugnon 7, Lausanne, 1005, Switzerland.

DM : University of Lausanne, Institut universitaire de formation et de recherche en soins, Biopole 2, Route de la Corniche 10, Lausanne, 1010, Switzerland.

Abbreviated Title: Adherence in CHH

Key Words: Kallmann syndrome, medication adherence, psychosocial factors, mixed methods, nursing

Disclosure Summary: The Authors have no disclosures to report

Word count: Text: 3935 Abstract: 247

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Corresponding author: Andrew Dwyer

Endocrine, Diabetes, & Metabolism Service

Centre Hospitalier Universitaire Vaudois

Rue du Bugnon 46

Lausanne, Switzerland 1011

Tel.: +41 079 556 60 1321 314 06 00

Fax: *+41 21 314 06 30*

E-mail: andrew.dwyer@chuv.ch

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Clinical Trial Registration: This study was registered at ClinicalTrials.gov (NCT01914172)

Precis: Men with congenital hypogonadotropic hypogonadism/Kallmann syndrome struggle with adherence to treatment and exhibit increased rates of depression. These patients suffer significant psychosocial consequences because of their condition. Patient-centered interventions promoting self-management may help bridge these unmet health needs.

Abstract

Context: Congenital hypogonadotropic hypogonadism (CHH) is a rare endocrine disorder characterized by absent puberty and infertility. Hormonal treatments are available to induce puberty and fertility in most these patients, yet little is known about patterns of adherence to treatment and the psychosocial impact of CHH.

Objective: To examine patterns of adherence to treatment, depressive symptoms, and illness perceptions of men with CHH. A secondary objective was to assess patient-reported barriers to adherence.

Design, Setting, and Subjects: A sequential, explanatory mixed-methods study involving both an online survey and three patient focus groups in an ambulatory setting.

Main Outcome Measures: Morisky medication adherence scale, Zung self-rating depression scale, revised illness perception questionnaire and patient-reported factors related to adherence. Comparisons were made with reference groups of community dwelling adults and other chronic conditions.

Results: A total of 101 men participated in the online patient survey (mean age 37$\pm$11 yrs). In total 58/101 had low medication adherence and 21/101 had moderate levels of adherence. Rates of mild, moderate and severe depressive symptoms (27%, 17%, 20% respectively) were significantly elevated compared to the reference population (all $p<0.001$). Illness perceptions indicated that CHH has significant negative psychosocial consequences on patients. Focus group participants (n=26) cited healthcare system, interpersonal, and personal factors as barriers to adherence.

Conclusions: CHH men are challenged to adhere to long-term medication regimes. They also face significant psychosocial morbidity that is often underappreciated by healthcare providers. Further work is needed to determine if patient-centered approaches can enhance self-management and coping.

Introduction

Congenital hypogonadotropic hypogonadism (CHH) is a congenital reproductive endocrine disorder resulting from deficiency of gonadotropin releasing hormone (GnRH) (Bianco & Kaiser, 2009). Hallmark clinical characteristics of this condition include incomplete-absent puberty and infertility. Additionally, there are a number of CHH-associated phenotypes that occur at variable frequencies including anosmia, eunuchoidal proportions, cleft lip/palate, and micropenis among others. Those patients with an impaired or absent sense of smell (anosmia) are termed as having Kallmann syndrome. CHH is a rare genetic condition thus making incidence difficult to accurately assess yet it is generally estimated at 1/4,000-10,000 (Fromantin et al., 1973). Further, the reported 2-5-fold male excess has no known genetic underpinning and likely represents a bias of ascertainment as women often present to gynecology rather than endocrinology practices. In most cases, CHH presents sporadically yet approximately one-third of cases display familial inheritance (Seminara et al., 1998).

Testosterone replacement for males (and estrogen for females) is commonly used to treat patients with CHH and to induce secondary sexual characteristics. From a provider point of view, testosterone gels, patches, and injections are safe, well tolerated, and highly effective for inducing virilization and normalizing sexual function yet they do not induce fertility (Han & Bouloux, 2010). However, specialized hormone treatment with pulsatile GnRH or exogenous gonadotropin therapy can induce sperm development in approximately 80% of men (Liu et al., 2009; Pitteloud et al., 2002). Notably, cases of spontaneous reversal have been reported in approximately 10% of cases (Raivio et al., 2007) but the vast majority of patients require lifelong hormone therapy. For chronic conditions like CHH, adhering to treatment and ongoing medical care can be problematic (Osterberg & Blaschke, 2005).

Indeed, a recent analysis of prescription claims for transdermal testosterone gels across multiple hypogonadism diagnostic codes indicates high discontinuation rates (Schoenfeld, Shortridge, Cui, & Muram, 2013). However, little is known about adherence patterns in men with CHH, who have severe testosterone deficiency resulting in absent sexual development and who have an absolute requirement for lifelong replacement.

Among chronic disease populations, both depression and patients' illness perceptions play important roles in adherence to treatment (Kucukarslan, 2012; Lin et al., 2004). Further, previous studies have shown that negative illness perceptions of patients with Cushing syndrome and acromegaly dramatically impact quality of life (QoL) (Tiemensma et al., 2011a, 2011b). However, as CHH is congenital, we do not know how patient perceptions may differ or not from other rare endocrine disorders. Two studies of treatment-naïve CHH adolescents have demonstrated increased levels of anxiety and depression compared to age-matched peers (Aydogan et al., 2012; Lasaite et al., 2013). These significantly impacted QoL measures (Lasaite et al., 2013), not all of which improved following 6-months of testosterone treatment (Aydogan et al., 2012). Thus, in the short-term at least, it appears that normalizing serum testosterone levels does not fully alleviate the psychosocial impact of the disrupted puberty of CHH. However, there are no available data on the psychosocial effects of CHH patients receiving long-term of treatment, how CHH patients perceive their condition, and how these aspects may relate to adherence to treatment.

Therefore, we aimed to examine adherence to treatment, depressive symptoms, and affective illness representations of men with CHH on long-term treatment. Further, we set out to identify the patient-reported barriers to treatment in order to develop interdisciplinary interventions to bridge the identified shortfalls and gaps in care.

Subjects and Methods

The Pender Health Promotion model was used as a guiding framework for understanding adherence among CHH men (Pender, Murdaugh, & Parsons, 2010). This study employed a sequential, explanatory mixed methods approach (QUANT-Qual) (Creswell, 2008). First, we conducted an online survey (QUANT) which included several previously validated instruments to assess adherence to treatment, depressive symptoms and illness perceptions. Subsequently, qualitative focus groups (Qual) were used to elaborate on the survey findings and to identify patient-reported barriers to adherence. The study was approved by the Cantonal Human Research Ethics Committee (Canton Vaud). Participants in the online survey provided an opt-in electronic consent while focus group participants provided written informed consent.

Subjects

CHH participants were recruited via the international network of clinicians and investigators studying GnRH deficiency (COST Action BM1105, www.gnrhnetwork.eu) and from existing patient support groups. As CHH is rare and affected male are 2-5 times more common than female cases (Seminara et al., 1998), men with CHH were targeted for recruitment. Adult males (18-70 years of age) who had at least one year of CHH treatment were included in the analysis of the online survey. A random sampling (40%) of participants were contacted to confirm CHH diagnosis and respondents with other forms of hypogonadism (i.e. Klinefelter syndrome or adult-onset hypogonadism), and those with less than one year of treatment were excluded. Focus groups were conducted in concert with CHH patient support meetings jointly coordinated by the investigators and patient community leaders.

Procedures

The online survey included collection of sociodemographics and questions regarding treatment and prior interactions with healthcare system/providers. Additionally, participants completed three validated questionnaires.

Morisky Medication Adherence Scale (MMAS): Patient reported medication-adherence was evaluated using the Morisky Medication Adherence Scale (MMAS) (Morisky et al., 2008). The 8-item questionnaire assesses different aspects of medication taking behavior such as forgetting to take medication, difficulty with maintaining a treatment plan, missing doses, intentionally stopping medication, etc. Scores can be categorized as low, medium, or high medication adherence. The MMAS is a widely used, reliable self-report instrument that has shown concordance with objective pharmacy refill records (Krousel-Wood et al., 2009) and has demonstrated good concurrent and predictive validity with 93% sensitivity and 53% specificity among patients taking medication for hypertension (Morisky et al., 2008). Unlike pharmacy refill records, MMAS captures events when medication has been dispensed yet not actually taken.

Zung Self-Rating Depression Scale (SDS)

This is a 20-item self-report instrument used to quantify severity of depressive symptoms across four distinct categories (affective, somatic, psychomotor, and psychological)(Zung, 1965). The SDS has been used extensively in healthy community dwelling adults and within patient populations, providing extensive validation data. It has been used to assess community base rates for depressive symptoms and as a rapid screening tool as well as a metric for evaluating treatment effectiveness (Blumenthal, 1975; Zung, 1990). The SDS is quickly administered and scores can be translated to four levels of depression symptoms: level 0 (no

significant symptoms), 1, 2 and 3 (mild, moderate and severe depressive symptoms respectively).

Illness Perception Questionnaire - Revised (IPQ-R)

The Illness Perception Questionnaire-Revised (IPQ-R) was used to assess both emotional and cognitive representations of illness (Moss-Morris, 2002). The IPQ-R includes 38 statements concerning views on the illness, scored on a 5-point Likert scale (from strongly disagree to strongly agree). The questions are transformed to seven illness perception dimensions: *timeline acute/chronic* (beliefs about the chronic nature of the condition), *timeline cyclical* (beliefs regarding the cyclical nature of the condition), *consequences* (negative consequences of the disease), *personal control* (perceived personal controllability of the disease), *treatment control* (perceived treatment controllability of the disease), *emotional representations* (the emotional responses generated by the illness), and *illness coherence* (personal understanding of the disease). A higher score indicates a stronger belief in that particular dimension.

Reference populations

Depressive symptoms (SDS) among CHH men were compared to community base rates for depressive symptoms previously reported in the literature. For the present study we utilized data collected from a group of 292 community-dwelling, healthy, employed men (mean age 36 yrs, range 25-49) (Barrett et al., 1978). This cohort of men underwent monthly administration of the SDS for a full year to determine prevalence rates of depressive symptoms among a non-patient, functioning population of untreated men.

As there are no normative scores for the IPQ-R for the general population, several reference groups were selected to provide clinical context for these data. We obtained reference values

in patients with long-term remission of acromegaly (Tiemensma et al., 2011a) as well as acute and chronic pain (Moss-Morris, 2002). The reference patients with long-term remission of acromegaly included 81 patients (47 men, 34 women, mean age 60 ± 12yrs). All patients had long-term biochemical control of acromegaly with a mean duration up 16 ±10 years. Because illness perceptions assess the perceptions of a specific disease, there are self-evidently no norm values for the general population, so scores of patients with acute and chronic pain have been used instead to provide meaningful context (Moss-Morris, 2002). The reference group with acute pain consisted of 35 subjects who were recruited from a private practice for physical therapy (20 men, 15 women, mean age of 36±12yr). These patients presented with a first-time peripheral painful injury that had been present for less than six weeks. The reference group of patients with chronic pain consisted of 63 subjects (26 men and 37 women, with a mean age of 54±11yr) who were recruited from hospital-based chronic pain clinics. All patients experienced pain for longer than three months which was unexplained by medical signs alone.

Patient Focus Groups

Focus groups were conducted to identify patient-reported barriers to health promoting behavior (adherence) among CHH men. We proposed the Health Promotion Model as a useful construct to explore adherence. It posits that thoughts, behavior, and environment must be considered as background factors that influence health behavior and that individuals engage in purposeful action if they value the outcome and perceive it as possible (Pender, Murdaugh, & Parsons, 2010). Focus group questions were formulated to stimulate discussion among the patients to elicit barriers to adherence to treatment (supplemental materials). Recordings of group discussions were transcribed, checked for accuracy and analyzed using NVivo10 (QSR International PSY Ltd., Melbourne Australia). Briefly, thematic analysis

(coding) was conducted by two separate investigators (AD:DM) to independently identify categories of responses and themes emerging from the focus group discussions to form a codebook. Discrepancies were discussed until resolution was achieved and iterative coding occurred until no further themes were identified, suggesting a saturation point had been reached. Additionally, connections between coded terms were mapped to examine connections within and between categories (i.e. whether or not certain themes appear together repeatedly) and those arising frequently and expansively were given particular emphasis (Saldana, 2009).

Analysis

Survey data are presented using descriptive statistics and comparisons between groups were performed using Student's t-test or Mann-Whitney rank sum test when not distributed normally. Linear regression was used to examine the possible effect of age at diagnosis or duration of treatment on medication adherence (MMAS). Z-Scores were used to assess differences in the proportion of CHH men exhibiting depressive symptoms (levels 1, 2, 3) compared to the reference group. Pearson product-moment correlations were performed to assess the associations between depressive symptoms (SDS), medication adherence (MMAS) and select illness-perception subscales (IPQ-R). The IPQ-R subscales were compared across the CHH and reference groups using ANOVA with Bonferroni post-hoc correction for multiple comparisons. Survey data were analyzed using PASW Statistics version 17.0.2 (SPSS Inc., Chicago, IL). All data are presented as mean ± SD and the level of significance for these analyses was set at $p \leq 0.05$.

Results

The web-based survey was online for 7-months and received 230 hits. In total, 101 men (mean age 37±11yrs, range 19-66, median 36) who completed the survey met the inclusion criteria and were retained for analysis. The sociodemographic information of the survey respondents is presented in Table 1. The age of meaningful diagnosis was variable ranging from neonatal diagnosis (n=4) to 32 years (mean 18±6, median 18 yrs). Notably, men with a familial pattern of inheritance (14/101, 14%) were not diagnosed earlier than sporadic counterparts (p=0.1) (Figure 1). Half the men had been seen at a specialized or academic medical center (52/101, 51%) and similar number had genetic testing performed (43/100, 43%) yet only 13% (13/101) had ever received genetic counseling. For pubertal induction, the age of initiating treatment ranged from 11-32 (mean 19±5, median 18 years). All men had been on long-term treatment (mean 18±12 yrs, range 1-46, median 16 years) and virtually all men (98/101) had reported having been on a form of testosterone treatment (injection, pellets, or gel) at some point. More than a third (37/101, 37%) reported having had fertility inducing treatment with either exogenous gonadotropins or pulsatile GnRH therapy with variable outcomes (Table 1).

CHH men are challenged to adhere to treatment

Results of the Morisky Medication Adherence Scale (MMAS) revealed a high percentage of men with poor medication-adherence. More than half (58/101, 57%) of the men had low levels of adherence, 21% (21/101) had moderate and a similar percentage (22/101) had high (exemplary) medication-adherence. A total of 93 men provided a self-reported longest-duration-off-treatment and responses ranged widely from never (n=24, 26%) to 15 years. Notably, 35/93 (38%) respondents reported being off treatment for more than one year. No associations were identified between longest duration off treatment and either age of

diagnosis (r=0.02, p=0.8), or the time since starting treatment (r=0.06, p=0.6). These data suggest that, despite notional availability of effective treatments and providers, men with CHH are challenged to stick with their medication regime.

CHH men exhibit high rates of depressive symptoms

One hundred CHH men completed the Zung Self-rating Depression Scale (SDS) and comparisons were made with the reference group of 292 similarly aged community-dwelling, employed men (mean age 36 years, range 25-49) (Barrett et al., 1978). The CHH patient population exhibited significantly higher rates of depressive symptoms (all $p<0.001$) (Figure 2). Twenty seven percent of CHH men had mild depressive symptoms, 17% moderate (i.e. dysthymia), and one in five (20%) exhibited the highest level of symptomatology (akin to major depressive disorder). Having more severe depressive symptoms was moderately correlated with poorer medication adherence ($R=0.35$, $p<0.001$). This is consistent with previous reports demonstrating that depression negatively affects adherence to treatment in chronic conditions like diabetes (E. H. Lin et al., 2004) yet it may also reflect the contrary - that patients with poorer adherence exhibit more depressive symptoms. Interestingly, while a high proportion of CHH men exhibit significant depressive symptoms, only one quarter (25/101) stated that their healthcare provider had ever discussed counseling services or had given them a psychological or psychiatric referral. Cumulatively, these data suggest that the psychological aspects of CHH are underappreciated and warrant renewed attention and assessment.

CHH men's illness perceptions reveal significant psychosocial consequences

Compared to reference groups, CHH patients viewed their illness as being more chronic (all $p<0.001$) and that their condition changes little over time, which is in contrast to chronic pain

which often has periodic flares ($p<0.001$)(Table 2). Furthermore, CHH men experience negative consequences impeding physical, psychological, and social well-being that were significantly greater than patients with acute pain and acromegaly (both $p<0.01$). Notably, this impact was positively correlated with depressive symptoms ($r=0.43$, $p<0.001$) and poorer medication adherence ($r=0.40$, $p>0.001$). The negative emotional impact (emotional representations) of CHH was not significantly different from patients with chronic pain, but significantly greater than patients with either acute pain or acromegaly (both $p<0.01$). These emotional representations were positively correlated with depressive symptoms ($r=0.64$, $p<0.001$) and weakly correlated with diminished adherence ($r=0.27$, $p>0.01$). Compared with patients in long-term remission of acromegaly, men with CHH perceived a higher level of personal control (perceived personal controllability of CHH) ($p<0.01$) yet treatment control (perceived treatment controllability of CHH) was perceived to be lower ($p<0.001$). Compared with patients with acute pain men with CHH perceived less personal and treatment control (both $p<0.001$). Lastly, men with CHH exhibited the highest scores on illness coherence (how they make sense of their condition) which may in fact be related to the congenital nature of CHH and that these men have lived with it since adolescence. However, illness coherence scores were negatively correlated with severity of depressive symptoms ($r=-0.37$, $p<0.001$) and thus may represent a protective or ameliorating factor for depression.

Healthcare systems, interpersonal influences, and individual factors pose barriers to adherence

Three focus groups were used to explore patient-reported barriers to health promoting behavior (medication adherence). Twenty six men participated (mean age 37±13yrs, range 18-66, median 36 years) and discussions revealed three, consistent, interrelated aspects of adherence including personal factors, interpersonal influences, and structural factors (i.e.

healthcare system) (Figure 3) . The most frequently reported facilitators of medication adherence included having a strong personal preference for a particular treatment modality, capacity for self-management (i.e. learning to self-inject medication), establishing a routine, having supportive family/peers, and understanding the importance of treatment for improving mood and limiting comorbidities. Commonly cited barriers to adherence included fractured healthcare transitions (i.e. changing providers and gaps in care) and pharmacy problems (i.e. difficulty obtaining syringes/needles and pharmacist concerns regarding anabolic abuse). Focus group participants reported that cognitive and affective factors such as depression, increased fatigue when off treatment and not having a good understanding of CHH, also negatively impacted their adherence. An additional theme emerging from discussions related to the initial treatment period of pubertal induction. Patients who did not understand the treatment plan (i.e. rationale for the timing of increasing the dose) or who had inappropriate expectations for treatment outcome (i.e. that testosterone would induce testicular growth) were less committed to adhering to treatment. These patient-reported outcomes underscore the importance of effective communication between healthcare providers and patients (Kovac et al., 2014) as well as the critical importance of anticipatory guidance during pubertal induction.

Discussion

Herein we report that men with CHH struggle with long-term adherence to treatment, exhibit increased incidence of depressive symptoms and have significant physical, psychological, and social consequences related to their GnRH deficiency. Psychological aspects such as depression and illness perceptions play important roles in how patients manage chronic health conditions (Kucukarslan, 2012; E. H. Lin et al., 2004). While there is no wide-reaching consensus on what is an acceptable or adequate level of adherence (Osterberg & Blaschke,

2005), these data indicate that only about one-quarter of CHH patients have excellent adherence (22% via MMAS and 26% reporting never having been off treatment). As testosterone replacement has potent effects on mood, libido and sexual function (Wang et al., 2004) we presumed that treatment pauses would result in a potent trigger for CHH men to resume treatment, yet this was surprisingly not the case. Further, non-adherence is relevant because, but for the rare cases of reversal (Raivio et al., 2007), patients require lifelong hormone replacement. In the present study, nearly 40% of men reported treatment pauses of a year or longer that not only diminish sexual function but can also cause anemia and increases the risk for developing osteoporosis (Finkelstein et al., 1987). Indeed, a report examining bone health in a cohort of Finnish CHH patients indicated that 9/26 (35%) had treatment pauses exceeding 5 years and exhibited significantly lower bone mineral density than those without gaps (Laitinen, Hero, Vaaralahti, Tommiska, & Raivio, 2012b). Further, meta-analyses demonstrate an association between low serum testosterone and the metabolic syndrome and diabetes (Corona, Monami, Rastrelli, Aversa, Tishova, et al., 2011; Ding et al., 2006). Thus, gaps in treatment may incur additional metabolic health risks. Indeed, acute withdrawal of treatment in CHH men induces increased fasting insulin levels and insulin resistance within two weeks (Yialamas et al., 2007) and men undergoing GnRH-analog induced androgen-deprivation therapy have increased rates of the metabolic syndrome and diabetes (Shahani et al., 2008). Thus, lack of androgen treatment or even inadequate replacement, appears to place CHH men at increased metabolic risk and potentially increased cardiovascular morbidity.

Beyond adherence problems, the CHH men in this study also exhibit significantly increased rates of mild, moderate, and severe depressive symptoms. These symptoms were correlated with poorer adherence which could reflect a bi-directional interaction. For instance, previous

studies of chronic disease patients support that depression negatively impacts adherence and health promoting behaviors (E. H. Lin et al., 2004). Conversely, given the potent impact of testosterone on mood (Wang et al., 1996), non-adherent CHH men may trigger depressive symptoms when they stop treatment. These interacting factors could perpetuate a vicious cycle of depression and non-adherence. While testosterone replacement seems to have an antidepressant effect in select subpopulations such as hypogonadal men with HIV/AIDS (Zarrouf, Artz, Griffith, Sirbu, & Kommor, 2009), the relationship between low testosterone and depression remains unclear. Concerning the psychological aspects of CHH, there is surprisingly limited literature with only three case series from 1964, 1971, and 1996. These studies reported on few subjects and describe issues related to anxiety, depression, and social difficulties among CHH patients, albeit in a rather ad hoc manner (Bobrow et al., 1971; Huffer et al., 1964; Huisman et al., 1996). These observations were reiterated in a recent patient narrative depicting ongoing struggles with lingering psychological aspects of CHH (Smith & Quinton, 2012). In the present study, we demonstrate the pervasive and lasting impact on mental health and quality of life in a large CHH cohort despite long-term treatment, albeit with variable adherence. Importantly, this largely goes under-recognized as only a quarter of men had a healthcare provider to discuss counseling or psychological/psychiatric support. Thus, this finding begs heightened attention and further studies investigating clinical depression and anxiety on a larger scale seem warranted.

The under-appreciation of psychosocial aspects of CHH may represent a clinician bias towards treating the physical signs of CHH. For instance, growth spurt, deepening of the voice and appearance of secondary sexual characteristics are easily observed and treated. These signs can serve as a rapid clinical barometer of response to treatment, whereas assessing emotional development and psychological adaptation are less easily quantified.

Further, providers may have limited availability of psychological referral sources. Regardless, it seems that CHH men have lasting psychological, emotional, and psychosexual aspects of their care that are largely unmet, a finding that is also supported by the affective illness representations of these patients. Importantly, illness coherence scores are inversely related to depressive symptoms suggesting that enhanced understanding of CHH could be protective factor for depression in these men and thus represents a target for interventions to enhance patient resilience. These patients perceive themselves to have a high level of personal control over their condition yet they have much lower ratings of treatment-control (how effectively their treatment controls their condition). This is in contrast to the prevailing opinion of healthcare providers and specialists, who see testosterone replacement in CHH patients as being highly-effective. When this was explored in the context of the patient focus groups, several themes consistently emerged as potential modifiable targets to enhance adherence including: improving anticipatory guidance (what to expect from endocrine treatment and during what timeframe), partnering for decisions on treatment modality (individual preferences), enhanced self-management (auto-injection), and sealing gaps in care (transitions between providers). These data support the utility of the Health Promotion Model as a theoretical framework for examining issues of adherence.

Along with all studies of this kind, this study has several limitations, including that the convenience sample for the internet survey may not be truly representative. However, studying rare disease populations is always challenging and, while this may not be a random sampling, it examines a relatively large cohort of such patients. Additionally, we assessed depressive symptoms and did not explicitly evaluate the actual incidence of clinical depression among this patient population. Moreover, the psychological aspects of chronic disease are complex and this study was not designed to delineate the relative contributions of

late diagnosis or body image problems related to CHH-associated phenotypes such as micropenis which are likely contributing variables. Self-report measures are not objective metrics, yet there has been a growing recognition and appreciation of their importance for managing chronic conditions (Bayliss et al., 2012). The objective of this study was to identify a group of CHH patients and explore their perspectives in detail to understand their health promoting behavior and perspectives in order to develop more-patient-centered approaches to care for these patients. Patients with CHH, like other chronic conditions, are responsible for the vast majority of their care. They decide whether to take medication or not, are the first to be able to identify changes in health status, and are the decision makers for making and keeping appointments with healthcare providers. Thus, understanding their unmet health needs, motivations, and perceptions regarding their condition are critical for developing approaches to enhance self-management.

In summary, patients with CHH are challenged to adhere to their long-term medication regimens and many have extended periods without treatment. In addition, these patients exhibit significant depressive symptoms and have long-lasting psychosocial effects that are often unappreciated by healthcare professionals. These mixed-methods findings underscore the likely benefit of early diagnosis, maintaining continuity of care through healthcare transitions, providing appropriate psychological support, and the need for patient education and anticipatory guidance related to testosterone treatment and possibility for developing fertility. These unmet health and informational needs warrant clinical attention and further work is needed to determine if patient-centered interventions can ameliorate these shortfalls in care.

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Tables and Figures

Table 1

Sociodemographic and treatment history of CHH men completing the online survey (n=101)

Age	**n**
19-29 yrs	30
30-39 yrs	38
40-49 yrs	19
50-59 yrs	11
60+ yrs	3
Education	
High school/vocational	35
University	35
Post-Graduate	31
Employment	
Working full-time	67
Working part-time	9
Unemployed	10
Retired	5
Student	9
No response given	1
Relationship Status	
Married	36
In a relationship	16
Single	24
Never been in a relationship	23
Divorced	1
No response given	1
Children	
none	75
biologic children	8
adopted children	18
Treatment	
testosterone (ever)	98
fertility treatment*	37
no children	22 (59%)
adopted children	7 (19%)
biological children	8 (22%)

*gonadotropin therapy or pulsatile GnRH

Table 2.

Comparison of IPQ-R scores between CHH patients and other patient groups

IPQ-R	CHH n=101	Acute pain n=35	Chronic pain n=63	Acromegaly n=81
Timeline (acute/chronic)	**26.7 (3)**	13.4 (5)**	23.1 (4)**	22.9 (6)**
Timeline (cyclical)	**9.7 (4)**	9.4 (3)	12.9 (4)**	10.1 (4)
Consequences	**21.3 (4)**	14.2 (4)**	23.5 (4)*	16.9 (5)**
Emotional representations	**19.2 (6)**	16.1 (4)*	19.8 (4)	12.6 (4)**
Personal control	**19.9 (5)**	22.9 (4)**	18.4 (4)	17.5 (5)*
Treatment control	**15.5 (4)**	19.4 (3)**	14.2 (3)	18.1 (3)**
Illness coherence	**18.1 (4)**	9.3 (3)**	13.4 (5)**	17.5 (3)

Data are mean (SD), * $p<0.01$ vs. CHH, ** $p<0.001$ vs. CHH

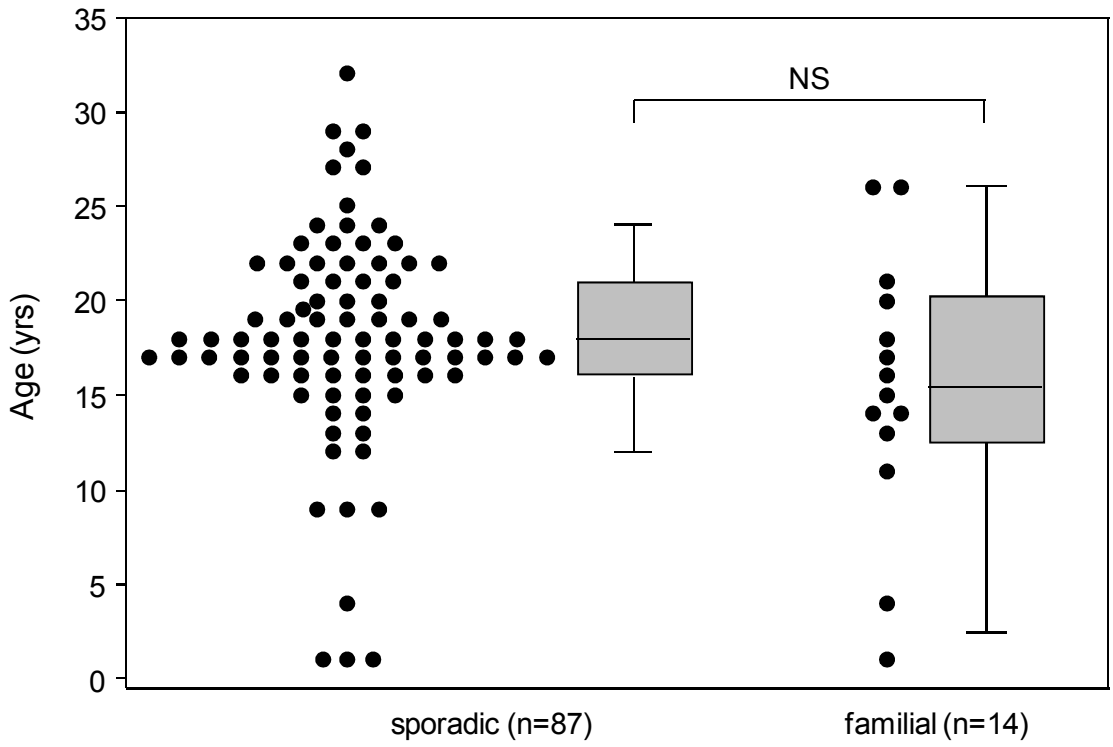

Figure 1. Age at CHH diagnosis

Figure Legend: Age of diagnosis of CHH among sporadic (n=87) and familial cases (n=14). The box depicts the 25-75th percentile and the horizontal line is the median. The error bars depict the 10th and 90th percentiles respectively. Age at diagnosis was not different between groups (p=0.1).

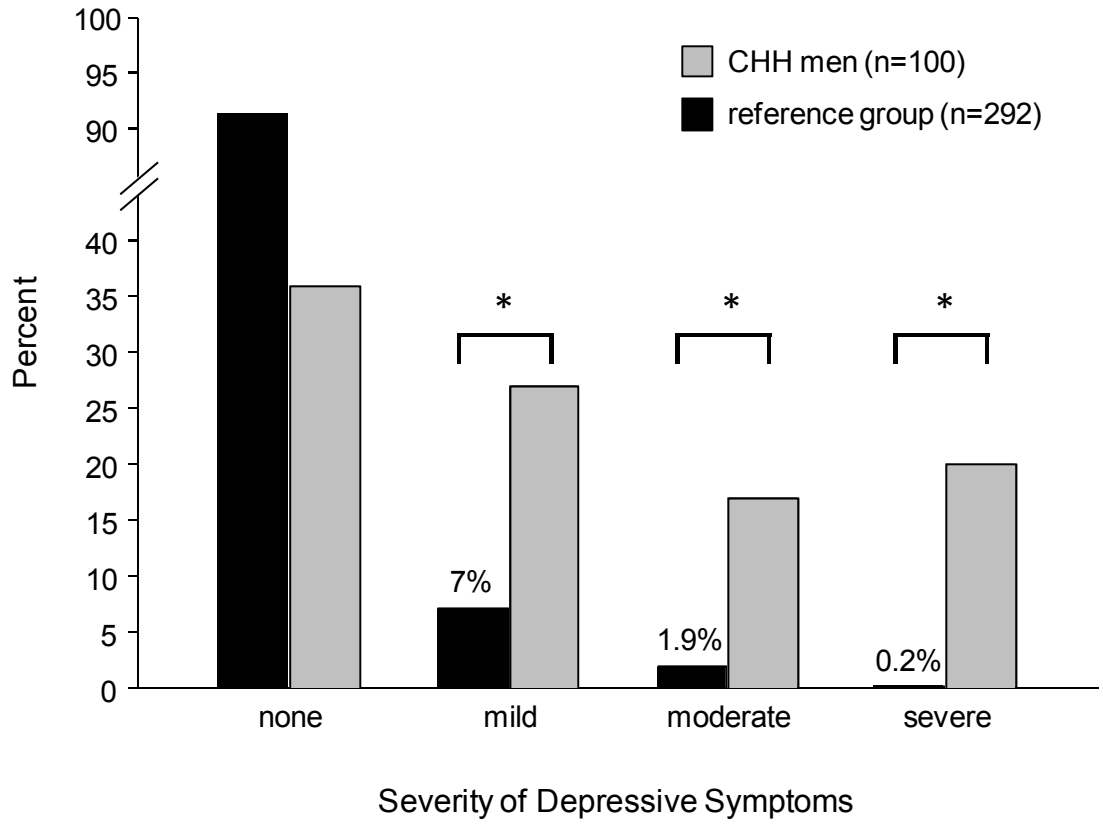

Figure 2. Severity of depressive symptoms in CHH men

Figure Legend: Depressive symptoms were assessed using the Zung Self-Rating Depression Scale. 27% of CHH men had mild symptoms (meaningful yet normally less than what would ordinarily initiate an evaluation or referral); 17% exhibited moderate symptoms (what one would expect to see among outpatient depression patients, or among patients with dysthymia) and 20% reported severe symptoms (characteristic of major depressive disorder). * $p<0.001$ vs. reference group (Barrett et al., 1978).

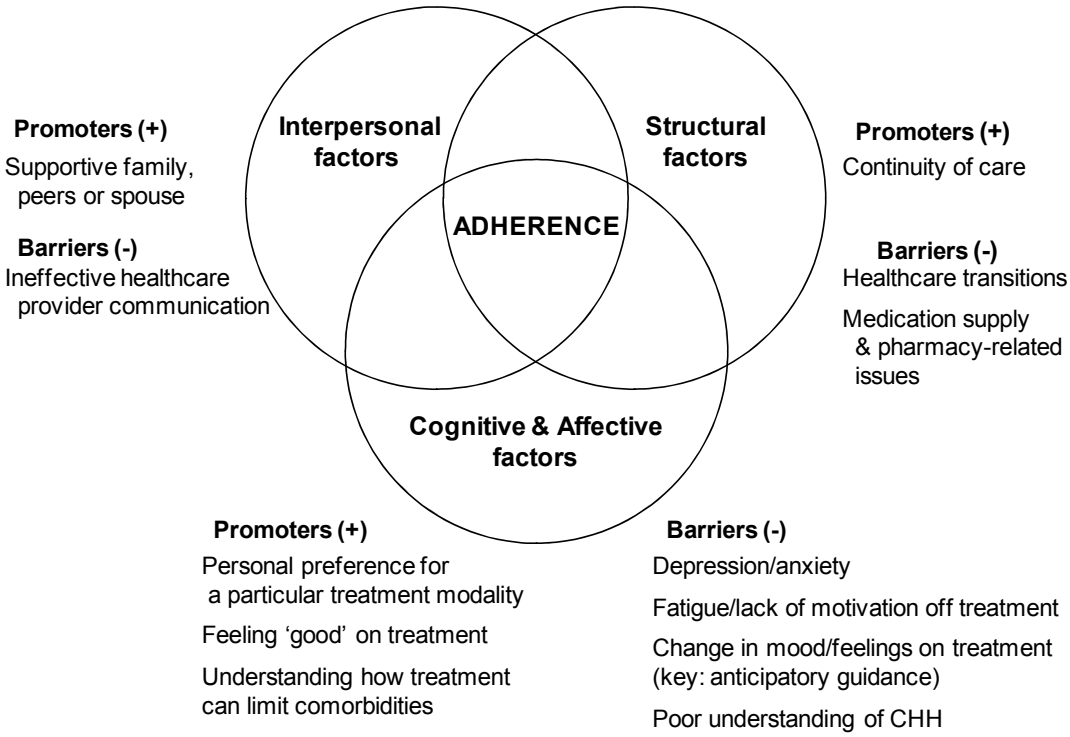

Figure 3. Patient-reported promoters and barriers to adherence to treatment

Figure Legend: Focus group participants identified three interrelated themes impacting adherence to treatment: interpersonal factors, structural factors (healthcare systems) and personal factors (cognitive and affective).

Supplemental Materials

Focus Group questions addressing promoter s and barriers to treatment adherence. As described in the Methods, focus group questions were derived from the Pender Health Promotion Model (17) and refined with input from patient community leaders.

1. CHH is a chronic condition and it is often hard to stick with treatment and keep appointments over time. Have you had periods when you were off treatment?
2. How do you feel when you are on/off treatment?
3. What do you think are the 3 most important things you need to do for your health related to CHH? What things prevent you from doing those things?
4. What do you think the benefits are to you in treating your CHH?
5. What are the things that keep you from sticking with your medication?
6. What are the things which help you staying on treatment?
7. Do you feel in control of your CHH medication?
8. Do you administer your own CHH medication? Would you like to? Are there things that prevent you from self-administering your CHH medication?

Article n°3

Authors, Title and Journal

Andrew A. Dwyer, Richard Quinton, Nelly Pitteloud, & Diane Morin

Psychosexual development in men with congential hypogonadotropic hypogonadism on long-term treatment: A mixed-methods study. *Journal of Sexual Medicine.* (Submitted April 14, 2014 - Confirmation of submission Appendix 12)

Affiliations

AD Endocrinology, Diabetes & Metabolism Service of the Centre Hospitalier Universitaire Vaudois, 46 Rue du Bugnon, Lausanne 1011, Switzerland ; University of Lausanne, Institut universitaire de formation et de recherche en soins, Biopole 2, Route de la Corniche 10, Lausanne, 1010, Switzerland

RQ University of Newcastle-upon-Tyne, Institute of Genetic Medicine and the Royal Victoria Infirmary, Newcastle-upon-Tyne NE1 3BZ, United Kingdom.

NP Endocrinology, Diabetes & Metabolism Service of the Centre Hospitalier Universitaire Vaudois, 46 Rue du Bugnon, Lausanne 1011, Switzerland ; University of Lausanne Faculty of Biology & Medicine, Department of Physiology Rue du Bugnon 7, Lausanne, 1005, Switzerland.

DM University of Lausanne, Institut universitaire de formation et de recherche en soins, Biopole 2, Route de la Corniche 10, Lausanne, 1010, Switzerland.

Corresponding Author

Andrew Dwyer, MSN, FNP-BC

Endocrinology, Diabetes & Metabolism Service

Centre Hospitalier Universitaire Vaudois

46 Rue du Bugnon, BH19.317

CH-1011 Lausanne,

Switzerland

Tel: +41 079 556 60 13

fax: +41 21 314 06 30

email: andrew.dwyer@chuv.ch

Conflict of Interest

The authors have no competing interests to declare.

Statement of Authorship

Category 1

(a) Conception & design: Andrew Dwyer, Nelly Pitteloud, Diane Morin

(b) Acquisition of data: Andrew Dwyer

(c) Analysis and interpretation of data: Andrew Dwyer, Richard Quinton, Nelly Pitteloud, Diane Morin

Category 2

(a) Drafting the article: Andrew Dwyer

(b) Revising it for intellectual content: Andrew Dwyer, Richard Quinton, Nelly Pitteloud, Diane Morin

Category 3

(a) Final approval of the completed manuscript: Andrew Dwyer, Richard Quinton, Nelly Pitteloud, Diane Morin

Abstract

Introduction. Congenital hypogonadotropic hypogonadism (CHH) is a rare, genetic, reproductive endocrine disorder characterized by absent puberty and infertility. Limited information is available on the psychosocial impact of CHH and psychosexual development in these patients.

Aims. To determine impact of CHH on psychosexual development in men on long-term treatment.

Methods. A sequential mixed-methods explanatory design. First, an online survey (quantitative) was used to quantify the frequency of psychosexual problems among CHH men. Second, patient focus groups (qualitative) were conducted to explore survey findings in detail and develop a working model to guide potential nursing and interdisciplinary interventions.

Main outcome measures. Patient characteristics, frequency of body shame, difficulty with intimate relationships and never having been sexually active were assessed. Additionally, we collected subjective patient-reported outcomes regarding the impact of CHH on psychological/emotional well-being, intimate relationships and sexual activity.

Results. A total of 101 CHH men on long-term treatment (>1 year) were included for the analysis of the online survey (mean age 37±11yrs, range 19-66, median 36). Half (52/101, 51%) of men had been seen at a specialized academic center and 37/101 (37%) reported having had fertility-inducing treatment. A high percentage of CHH men experience psychosexual problems including difficulty with intimate relationships (70%), body image concerns/body shame (94/101, 93%), and the percentage of men never having been sexually

active is 5-times the rate in a reference group (26% vs. 5.4%, $p<0.001$). Focus groups revealed persisting body shame and low self-esteem despite long-term treatment that has lasting impact on psychosexual functioning.

Conclusions. CHH men frequently experience psychosexual problems that pose barriers to intimate relationships and initiating sexual activity. These lingering effects cause significant distress and are not ameliorated by long-term treatment. Psychosexual assessment in CHH men with appropriate psychological support and treatment should be warranted in these patients.

Keywords

Kallmann syndrome, psychosocial factors, body image, self-esteem, psychosexual outcome, nursing, mixed methods, congenital hypogonadotropic hypogonadism

Introduction

Congenital deficiency of hypogoandotropic hypogonadism (CHH) is an endocrine disorder resulting from gonadotropin-releasing hormone deficiency (GnRH). This genetic condition is clinically characterized by absent puberty and infertility and may be accompanied by a variety of associated phenotypes including cryptorchidism, micropenis and anosmia (termed Kallmann syndrome) (Bianco & Kaiser, 2009). CHH is rare with incidence estimated at 1 in 4,000-10,000 (Fromantin et al., 1973) and has a striking gender discordance (approximately 2-5 males for each female case) (Quinton et al., 2001; Seminara et al., 1998). This gender difference remains genetically unexplained and may well represent an ascertainment bias as amenorrheic women presenting for gynecologic evaluation may likely receive empiric treatment, as opposed to being referred for an endocrine evaluation (Mitchell et al., 2011). Importantly, CHH patients cannot initiate puberty spontaneously and require hormonal

treatment to develop secondary sexual characteristics (Han & Bouloux, 2010). It is a treatable form of infertility with approximately 80% of men able to develop sperm with either pulsatile GnRH or exogenous gonatropin therapy (Liu et al., 2009; Pitteloud et al., 2002).

CHH patients typically present to medical attention with failure to undergo spontaneous puberty; the challenge being to differentiate this rare condition from more frequent variants in the timing and onset of puberty such as constitutional delay of growth and puberty(Harrington & Palmert, 2012; Palmert & Dunkel, 2012). CHH adolescent males presenting with absent puberty after 14 years of age, may be inaccurately defined as "late bloomers" and their treatment unnecessarily delayed; the "watchful waiting" approach finally ending with the patients re-presenting as apubertal young adults with frank hypogonadotropic hypogonadism (Young, 2012). As captured in a recent patient report, such delays in diagnosis can have lasting psychological and emotional effects on patients (Smith & Quinton, 2012).

Puberty is a developmental process characterized by numerous physiologic, psychosocial, and emotional changes culminating in reproductive capacity. While timing of onset of pubertal development is variable, late sexual development can carry a psychological burden. Delayed puberty can result in body image concerns, low self-esteem and social isolation and later sexual activity (Golub et al., 2008; Michaud et al., 2006; Waylen & Wolke, 2004). Further, many late maturers experience victimization or bullying, which are important and common risk factors for developing depression (Thapar et al., 2012). For CHH men, who represent the most extreme form of delayed puberty, data on psychological aspects are limited to a handful of descriptive case series with few patients (Bobrow et al., 1971; Huffer et al., 1964; Huisman et al., 1996). Prior to starting treatment, adolescents with CHH exhibit impaired quality of life and increased anxiety and depression compared to peers (Aydogan et al., 2012; Lasaite et

al., 2013). However, the existing literature has solely focused on the time of diagnosis or during the initial pubertal induction and therefore, data regarding the psychosocial impact of CHH in men on long-term treatment are lacking. Accordingly, we do not know whether long-term sex steroid treatment and/or fertility-inducing treatments mitigate the impact on psychosexual development of CHH men.

Aims

This study aimed to examine patient characteristics, sexual activity and frequency of body image concerns among men with CHH. Further, we aimed to explore the psychosocial impact of CHH on body image and psychosexual development in CHH men on long-term treatment.

Methods

A community based participatory research framework (N. B. Wallerstein & Duran, 2006) was utilized for developing and conducting this sequential, explanatory mixed-method study (Creswell, 2008). In the context of a European network focused on CHH/KS (COST Action BM1105), partnerships with patient community leaders (i.e. moderators of online patient support sites) were developed to include patient perspectives into the process. Patient leaders participated in developing and improving the language and clarity of the survey, facilitated recruitment efforts, and provided feedback on study findings at each stage of anlaysis. First, a quantitative online survey was used to collect patient characteristics and information on diagnosis/treatment as well as body image, relationship status and sexual activity. Subsequently, qualitative patient focus groups were conducted to explore the survey findings in greater detail. Focus groups were held in concert with CHH patient support meetings jointly planned by patient community leaders and study investigators. The psychosexual assessment of men with CHH was part of a larger research project examining health

promoting behavior (Pender, Murdaugh, & Parsons, 2010) and factors affecting quality of life among CHH men. The ultimate goal of this study is to design innovative nursing and interdisciplinary interventions to address unmet health needs in these dispersed rare disease patients. The study was approved by the Health Research Ethics Committee (Canton Vaud) and all participants provided informed consent prior to the initiation of study-related activities. For the online survey, an opt-in electronic consent was used while focus group participants provided written informed consent.

Subjects

As male patients outnumber female patients in this rare disorder (Seminara et al., 1998) we focused our attention on male subjects. Adult CHH men (18-70 years) on treatment for at least 1 year were recruited for the study. A random sampling (40%) of online survey respondents were contacted and interviewed to confirm diagnosis. Those men with other causes of hypogonadism (i.e. Klinefelter syndrome, adult-onset hypogonadism) were excluded and surveys with multiple incomplete or conflicting responses were excluded. The study was publicized online via a closed/private CHH/KS social media group (Facebook), CHH/KS forum (chat room), a clinical trials registry, and the COST Action website. Data from the American National Survey of Sexual Health and Behavior was used as a comparison reference group (Leigh et al., 1993).

Statistics

Survey results were analyzed using descriptive statistics (mean ± standard deviation, range, median), Student's t-test (Wilcoxon rank-sum test for data not normally distributed) to evaluate differences between groups, and Z score to assess differences in proportions between

the CHH and the reference group. SigmaStat (Systat Software Inc., San Jose, California, USA) was used for statistical analyses and a $p<0.05$ was considered significant.

Qualitative Analysis

Thematic analysis (coding) of focus group transcripts was performed by two separate investigators (AD:DM) using NVivo10 (QSR International PSY Ltd., Melbourne Australia). Categories of responses and themes were first classified on the basis of the Health Promotion Model (Pender, Murdaugh, & Parsons, 2010. Iterative coding occurred until no further themes were identified, suggesting a saturation point had been reached. Additionally, connections between coded terms were mapped to examine connections both within and between categories (i.e. whether or not certain themes appear together repeatedly) and those themes arising frequently and expansively were given particular emphasis (Saldana, 2009).

Main outcome measures

For the online survey, patient characteristics, frequency of body shame, difficulty with intimate relationships and never having been sexually active were the main outcome measures. For patient focus group discussions, subjective patient-reported outcomes regarding the impact of CHH on psychological/emotional well-being, intimate relationships and sexual activity were recorded.

Results

The survey was online for 7 months and received a total of 230 hits of which 101 surveys (44%) were retained for analysis. The men (mean age 37±11yrs, range 19-66, median 36) had all been on long-term treatment (>1 year) and half (52/101, 51%) had been seen at a specialized or academic medical center. Participant characteristics and treatment information are presented in Table 1. In this cohort, CHH was diagnosed neonatally in four men and as

late as 32 years (mean 18±6, median 18 years). The age of initiating treatment to develop secondary sexual characteristics ranged from 11-32 years (mean 19±4, median 18 years) and nearly all men (98/101) had been on some form of testosterone replacement (injection, implanted pellets, patches, or gel). Over a third of men (37/101, 37%) reported having had fertility inducing treatment (exogenous gonadotropins or pulsatile GnRH therapy) with variable outcomes (Table 1). Nearly a quarter of the men receiving fertility-inducing treatment (8/37, 22%) were single or had never been in a relationship, suggesting a motivation for pursuing these time and resource-intensive programs extended beyond an immediate desire to achieve fertility.

Despite long-term treatment, a high proportion of CHH men have psychosexual problems

As no data are available on the sex lives of men on long-term treatment, we asked participants if they had ever been sexually active. Notably, 26/101 (26%) of men reported they had never been sexually active. This is nearly 5-times the rate (26% vs. 5.4%, $p<0.001$) observed in adult men (18+ years) in a large ($n>2,000$) probability survey examining sexual activity (Leigh et al., 1993). During survey development, discussions with patient community leaders suggested that traumatic experiences, body image concerns, and difficulty with intimate relationships were frequently raised in private, online discussions. When we inquired about these points 72% (73/101) stated that they had been teased or ridiculed because of CHH and 93% (94/101) reported that they had felt embarrassed or ashamed of their body and avoided undressing in public such as at the gym or beach. Further, 70% (69/99) men agreed that intimate relationships were difficult because of CHH. Neither age of diagnosis nor age of treatment initiation were significantly related to any of these results. We hypothesized that concerns about testicular size could be a factor in these findings, yet no differences were

observed between those men who had received fertility-inducing treatment (inducing testicular growth) and those men on testosterone only (no testicular development). These data point to a significant impact of CHH on the psychosexual development. To explore this in greater detail, we conducted three patient focus groups. These discussions provided further insight into the survey findings and helped explain the lasting psychosexual impact of CHH that pose barriers to dating, developing intimate relationships and initiating sexual activity.

CHH-related body shame has lasting impact on psychosexual functioning

Patient focus group discussions grew from two questions: "What has been the most difficult part of living with CHH?" and "How has CHH affected your sex life and intimate relationships?". Twenty six men participated in the focus groups (mean age 37±13yrs, range 18-66, median 36 years) revealing consistent, overarching themes of shame and isolation related to CHH. More specifically, patients reported their sense of isolation resulted from their absent sexual development and feeling "left behind" as peers developed physically, became sexual active, and assumed adult roles (Figure 1, Table 2). This marginalization fed fears of being exposed and many (20/26) attempted to hide their lack of puberty by avoiding situations possibly involving nudity and in some cases avoiding social events. Problems with body image dominated focus group discussions both in terms of the number of comments and the proportion of participants (23/26) reporting body shame (Figure 1, Table 2).

Similar to the literature on late maturing adolescent boys (Golub et al., 2008; Michaud et al., 2006; Thapar et al., 2012; Waylen & Wolke, 2004) and the online survey results, men in the focus groups reported traumatic experiences including teasing, victimization and bullying related to their youthful appearance, under-developed genitalia and in some cases gynecomastia resulting from CHH. Notably, despite virilization on long-term hormone

treatment, these men struggled to overcome a self image of the undeveloped, youthful adolescent of their past. These negative thoughts persisted well into adulthood - even though many realized that these thoughts were not rational. Discussions revealed a cycle of isolation and shame wherein hiding and removing oneself from social situations only worsened the body image and self-esteem issues (Figure 1, Table 2).

Importantly, patients reported ameliorating factors that helped them cope with their disrupted psychosexual development including meeting other patients with CHH (Table 2). In total, 15/26 men provided unsolicited comments stating that this was a life-changing event enabling them to overcome some of their feelings of shame and isolation. Half of the men (13/26) shared that coping with the psychosexual aspects of CHH became easier with age and that this was often related to finding someone who accepted them as they are (i.e. an understanding healthcare provider, therapist, partner, or spouse). These highlight potential interventions such as connecting patients for peer-to-peer support.

Limitations

This type of study has inherent limitations. First, studying rare disease populations pose challenges for recruiting patients (Kruer & Steiner, 2008; Watson et al., 2008), which tends to limit sample size. We attempted to overcome this by using web-based data collection via an online survey. This approach introduces potential bias as not everyone has internet access, so this convenience sample may be enriched with well-educated men and may reflect a response bias of more proactive and/or more severely affected patients. Second, as no validated questionnaire is available for CHH men to assess health related quality of life or sexual function (Langham, Maggi, Schulman, Quinton, & Uhl-Hochgraeber, 2008), we developed our own questionnaire. Face validity was sought with input from patient advocates, but a full

validation process was not performed. While validity and reliability in self-report responses are important, there is a growing acceptability of using patient-reported outcomes for managing chronic conditions (Bayliss et al., 2012). Further, using focus groups with expert patients to explore these is an added value to the validity of the results.

Discussion

We report evidence of persisting psychosexual impact of CHH that is not ameliorated by long-term hormone replacement therapy. CHH is a rare disorder that has been previously been used as a unique human disease model providing important insights into the hormonal control of the hypothalamic-pituitary-gonadal axis (Pitteloud et al., 2008a, 2008b). Further, genetic studies on this extreme form of delayed puberty have informed our understanding of the molecular control of human puberty and reproduction (Balasubramanian et al., 2010; Bianco & Kaiser, 2009). However, there are scant data on how the severe disruption of puberty impacts psychosexual development in CHH men.

Previous reports on the psychosocial aspects of CHH include several descriptive case series of small cohorts CHH men during initial treatment. The 1964 report of 8 cases of so-called 'sexual infantilism' (including 3 CHH men 20-47 years of age) commented on embarrassment because of youthful appearance and feelings of sexual inadequacy (Huffer et al., 1964). A subsequent 1971 report documenting 13 cases from the Johns Hopkins University Hospital added observations on insecurity, decreased confidence and low interest in dating among 13 CHH men (19-44 years old) after starting treatment (Bobrow et al., 1971). Another study published in 1996 followed 8 CHH men initiating pulsatile GnRH therapy for pubertal induction noting diminished social interactions and poorer views of their physique compared to controls (Huisman et al., 1996). In the present study, we examined these issues in a

relatively large cohort of CHH men (n=101) providing data on the prevalence of these issues. We then conducted focus groups to develop an explanatory model for these observations, thus enhancing our understanding of the unmet psychological and psychosexual needs of CHH men in order to better direct therapy and interventions.

In contrast to prior studies, we focused exclusively on men receiving long-term treatment to see if psychosocial and psychosexual issues are corrected by a longer period with a normalized sex steroid milieu. Testosterone replacement therapy has long been shown to be effective for inducing secondary sexual characteristics and normalizing sexual function (Han & Bouloux, 2010)and has well-documented beneficial effects on muscle and fat-free (lean) body mass (Bhasin et al., 1997) as well as mood (Wang et al., 1996). Importantly, the data presented herein suggest that normalizing serum hormone levels does not ameliorate the psychosocial consequences of CHH. Moreover, focus group discussions revealed CHH men are challenged to perceive themselves as a normal-appearing virilized men. This may relate to a form of body dysmorphic disorder (BDD) wherein individuals develop an altered view of personal appearance (Kaplan, Rossell, Enticott, & Castle, 2013). BDD has been linked with early traumatic life events (Buhlmann, Marques, & Wilhelm, 2012) and can have significant impact on quality of life (IsHak et al., 2012). As BDD appears to be responsive to cognitive-behavioral interventions, similar approaches may be warranted for CHH men to address their significant body image concerns.

A surprising finding was that fertility was never raised as a major concern within focus group discussions. Rather, attention centered on body shame and lack of genital development. Testosterone replacement induces secondary sexual characteristics and normalizes sexual function yet has no effect on testicular development and testis volume remains small (infantile

in some cases). We found that 22% of men who had received fertility-inducing treatment had never been in a relationship. This observation suggests that these treatments were pursued to augment testicular volume and thus normalize genital appearance. Indeed, it would be interesting to utilize the recently developed genital self-image scale (Herbenick, Schick, Reece, Sanders, & Fortenberry, 2013) to better understand how these factors may contribute to these men's sexual experiences and why they are 5-times more likely to never have been sexually active. Some have speculated that the atrophic testes and/or severely diminished phallus size sometimes associated with CHH as can have serious negative effects on self-confidence and the sexual life of CHH men (Han & Bouloux, 2010; Bouvattier, et al, 2012; Young, 2012). Herein, we provide direct evidence supporting these assertions.

Micropenis (with or without cryptorchidism) can be associated with CHH. We did not assess how many men were born with micropenis as this can difficult to ascertain in the absence of medical documentation. However, outcome studies of patients with micropenis indicate diminished penis size persisting into adult life can have negative consequences on sexual quality of life (Callens et al., 2013). Related to this, concern about penis size was pervasive and a frequently occurring topic in focus group discussions. Indeed, in every focus group patients made spontaneous inquiries regarding normative ranges for penis size among CHH men. While population-based normative data are available on penis size (Herbenick, Reece, Schick, & Sanders, 2014) corresponding data on a large cohort of CHH is lacking. CHH men experience significant preoccupation and shame regarding penis size. Accordingly, it could be useful to evaluate this using a validated instrument (Veale et al., 2014) before and after providing reference ranges for this patient population along with targeted cognitive-behavioral interventions to address these body shame issues. Such an approach could be a possible avenue for alleviating this distressing problem for CHH men. The ultimate goal of

this study was assess impact of CHH on psychosexual development in order to identify patient needs and design innovative nursing and interdisciplinary interventions for these dispersed patients. Importantly, one result of this study was that conducting patient focus groups brought together isolated patients and provided them with an opportunity to discuss these problems, share experiences and seek support – which in and of itself was an important and empowering intervention for these patients.

Conclusions

This mixed-methods study presents data demonstrating the pervasive psychosexual difficulties experienced by CHH men on long-term treatment. The CHH-related absent sexual development has lasting effects that pose barriers to intimate relationships and initiating sexual activity. Further, the psychosocial distress experienced by CHH men is not ameliorated by long-term treatment. These findings underscore the importance of psychosexual assessment of CHH men and the need for psychological support and interdisciplinary care for this patient population.

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Tables

Table 1

Sociodemographic and treatment information of CHH men (n=101)

Age	**n**
19-29 yrs	30
30-39 yrs	38
40-49 yrs	19
50-59 yrs	11
60+ yrs	3
Education	
High school/vocational	35
University	35
Post-Graduate	31
Employment	
Working full-time	67
Working part-time	9
Unemployed	10
Retired	5
Student	9
No response given	1
Relationship Status	
Married	36
In a relationship	16
Single	24
Never been in a relationship	23
Divorced	1
No response given	1
Children	
none	75
biologic children	8
adopted children	18
Treatment	n (%)
testosterone (ever)	98
fertility treatment*	37
single/never been in a relationship	8/37 (22%)
no children	14/29 (48%)
adopted children	7/29 (24%)
biological children	8/29 (28%)

*gonadotropin therapy or pulsatile GnRH

Table 2.
Themes and representative quotes arising from focus group discussions

Theme	Representative quotes
Feeling left behind (isolation)	• "I was diagnosed at 23. So, that's why I say I 'missed out' on that 17-20 (years of age) physical and emotional development. I think that is where people miss-out on a lot... and not being able to catch up" • "...watching your sisters, your younger sisters and younger cousins and watching them pass you while you are left behind right now is still emotionally traumatic. It's just the little stuff like that... it all builds" • "I was dependent on a nurse who injected my treatment twice a week, and people all around me experiencing their young adult life...independence from parents, sentimental and sexual relationships, a night out... all that discovery was out of reach for me for unfair reasons"
Fear of being exposed	• "Fear of exposure was the biggest thing for me… especially when I was younger in middle school and through high school. I was afraid to go into the bathroom and pee in the urinal" • "(around 15 years-old) I was forced to take gym class and I feared that I would be noticed. I knew I would be ridiculed mercilessly if anyone found out. I vowed that I would not use the shower after gym class no matter what" • "(communal showers) it was like doing anything to get out of a shower... I would try anything. In fact, I would just come out of the gym and just not shower. You know, just put my clothes on over my gym shorts and stuff like that. But it's that…fear of exposure" • "I would purposefully forget (gym clothes) so I wouldn't have to take physical education so I wouldn't have to shower. And the teacher would go to the lost property and find a spare and try to force me to wear it so that I could take part. So, I would be in detention…god knows how many times"
Hiding	• "(during teen years) I was doing my best to remain as inconspicuous as possible and not have my condition discovered… nothing else mattered" • "You spend so much of your adolescence and your late teens, 20s hiding stuff. You are hiding the fact that you can't smell, you are kind of covering over that, you are hiding that you don't want to shower, it's just so much hiding that there's almost an emotional reticence. And, I think that translates into relationships too" • "For me it has been shame. Yeah, that has been the hardest part. And so... I kind of isolated myself, staying indoors, and that has led to a kind of social anxiety. So, I don't really have any friends really…that's given the most impact on my life"
Body shame/ poor body image	• "I haven't been intimate with anyone in over 10 years. I don't have any friends, I don't have a girlfriend…I have kind of accepted that I won't have any girlfriends or friends. I'm just ashamed of my body" • "(regarding dating) you think down the road and wonder if this eventually goes anywhere... I don't want to undress in front of this person"

Body shame/ poor body image	• "My biggest thing was about having Kallmann's (CHH) was genital size. That's the only thing that was affected…and been an issue. Which I know is very superficial and is probably a bit silly, but that's me. It's always sort of there, you're always sort of consciously • aware of it" • "There's extreme shame about having small genitalia…it's just extreme for me" • "we are probably hung a bit less-well than most people. It can be a bit…you know, if a woman…if you drop your trousers and a woman bursts out laughing, it's just devastating. What do you do?" • "I was always ashamed of that stuff (body & gynecomastia). It was insidious, sometimes I was seen as a girl…you know, is that a boy or a girl?"
Low self-esteem	• "I felt ashamed really… I withdrew from it, from everything really. So, it's the same I don't really have any friends really, not a lot of social contact or anything like that" • "It (CHH) is always with me... very, very low self-esteem, massively low confidence…you know, I have done all the educational stuff, I've got a good job. Even after 20+ years with the same company, my confidence level at my work is still very, very low. I tend to mask it sometimes, in that sort of situation but in reality, I'm in quite a fragile state…it doesn't take much to sort of push me down" • "For a long time even after starting treatment,I knew I was physically as normal as a man can be...(but) I was unable to seduce a woman... very difficult to deal with the potential rejection... still thinking she would see a kid who should not do what he is doing. I had a total lack of confidence in this aspect of my life"
Lingering effects	• "All of those things are seeds for psychological damage. I mean the stuff occurring at that stage builds up and builds up and builds up over the years…it lingers for sure" • "You may have all the outward appearances (of puberty), but here (pointing to head)… as far as I'm concerned, I'm still different. It's almost as though one day, someone is going to see right through it, and they'll know…it's that fear." • "Basically as a Kallmann (CHH) patient I spent most of my early adult life building barriers and walls to others to avoid being emotionally hurt and keep mental sanity. It worked... but later on in my life, these survival skills were totally irrelevant and became the main problem" • "I still have a hard time with public nudity... I wouldn't join a gym that had an open shower... so like there are even these lingering psychological that affect me even today but they are not as severe as when I was younger" • "I'm wondering is if we have some overlap with a PTSD (post traumatic stress disorder), there might be some things that are still things that will trigger flashbacks" • "I was forever looking back at as far as I could see... a lost 16 years. As I've grown older, it's not just the 16 years. There's actually a lot, lot more than that. The older I get, the focus is perhaps not on looking back but looking forward. And that…is just as negative for me sometimes as it is looking back. As far as I'm concerned, it never, ever leaves me…"

Mediating factors	• "I have found the groups on Facebook and that, you know... starting to talk to people. That's the only thing that has really helped me so far for coming to terms with it (CHH)" • "It wasn't until I found other people like (patient community leader) and such that I kind of filled in the blanks a bit. It was quite isolating for me and I had no one to talk to and I felt like I was the only person in the world to have this problem you know?" • "The two major things for me have been having somebody love me and not see as no different from any other man…and this, meeting other people face to face, being able to talk and email people and just... you know…(other patient) has been exceptionally caring to me" • "When I was in my teens and 20s it was harder... it does get a little easier, but still there's a lot of emotional scars" • "It's like, you can answer those questions(for young CHH patients) and say: look, it's going to be tough for a couple of years…but, you know, it's going to get better" • "Learning about it (CHH) made me feel that Kallmann (CHH) is not such a big deal. But in my case, it was not enough and the psychotherapy aspect helped a lot... I'm not sure I'd be as satisfied without"

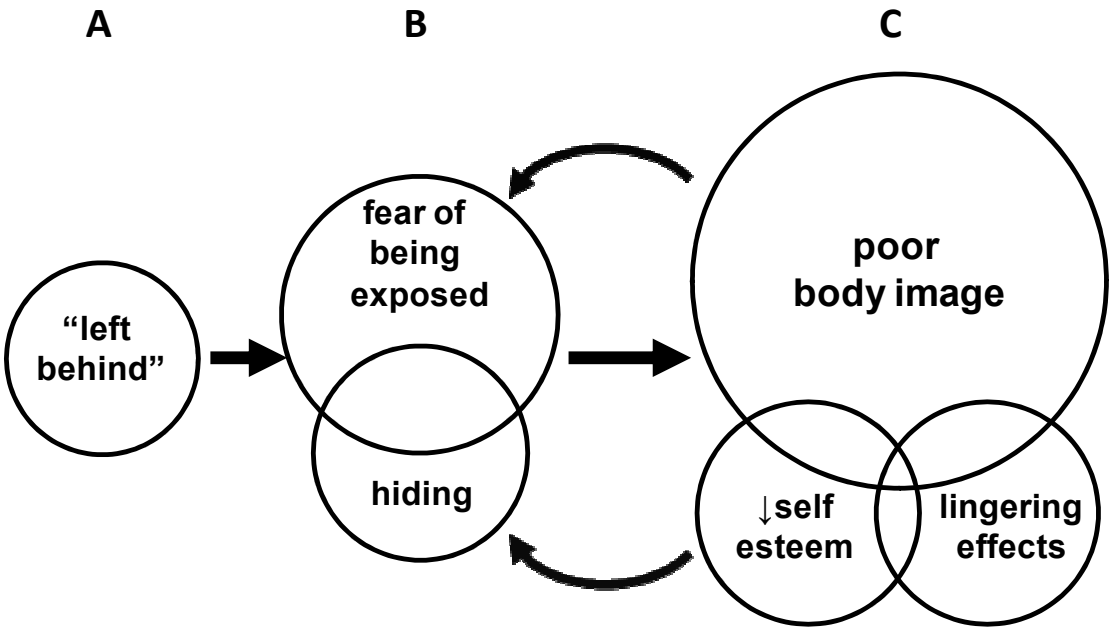

*Figure 1***.** Focus group themes related to the impact of disrupted sexual maturation on psychosexual development and intimate relationships.

Figure Legend: (A) focus group participants reported feeling isolated and "left behind" as peers underwent sexual development, started dating, and began taking on more adult roles. (B) patients often developed fear and anxiety about being exposed and tried to hide their lack of sexual development as a coping response. (C) body shame and body image concerns were the most frequently cited issues which co-occurred with low self-esteem. These issues interacted with existing fears/anxiety creating a cyclic pattern with effects lasting far after treatment initiation. Circles depict themes from focus group discussions, circles are sized proportionally with the number of references, overlapping circles depict co-occurring themes and interactions are noted by arrows.

Chapter V: Discussion

Rare diseases can be characterized as conditions with low prevalence and high complexity. And while individually infrequent, collectively the estimated 5,000-8,000 rare diseases have a large cumulative effect - impacting approximately 30 million Europeans (van Weely & Leufkens, 2004). As described in the EURORDIS report (EURORDIS, 2009), patients with rare diseases face a number of challenges that place them in the realm of health inequities (Holtzclaw Williams, 2011). These so called orphan diseases are often neglected and thus, there was little available data on adherence in CHH patient populations, the psychosocial impact of this rare endocrine disorder, or the unmet health and informational needs of this patient population. This was the impetus for this nursing needs assessment study with the ultimate goal of identifying targets for nursing and interdisciplinary interventions to meet shortfalls in care for these patients. The three publications presented in the results chapter address each of the four specific aims. However, that does not capture the full picture of this project as this thesis contributes to nursing knowledge in several important ways.

Identifying unmet health and informational needs of CHH men

Rare diseases such as CHH are chronic health conditions and require lifelong treatment. However, adherence to treatment is a significant challenge for managing chronic diseases (Osterberg & Blaschke, 2005) yet combing the CHH literature identified only two reports with a combined 41 subjects suggesting that one quarter to one third of CHH patients have problems with adherence (Huffer et al., 1964; Laitinen et al. 2012). Herein, this study demonstrates the extent of adherence problems is much larger - only approximately 25% of CHH men have high levels of adherence and the vast majority struggle with adherence to long-term treatment. These data identify adherence as a significant barrier for effective long-term disease management. Subsequently, we conducted focus groups (utilizing the HPM

framework as a guiding theory) and identified modifiable patient-reported barriers to adherence that are targets for nursing interventions.

It has been documented in the literature that both depression and patients' perceptions of their condition can have significant impact on adherence (Ciechanowski et al., 2000; Kucukarslan, 2012; Lin et al., 2004). Accordingly, we examined these characteristics as correlates of adherence and show that CHH men have significant negative psychosocial/psychological/psychosexual consequences from CHH. These data should spark renewed attention as they provide evidence of persisting psychological impact that is not ameliorated by long-term hormone replacement therapy. CHH has been previously been used as a unique human disease model providing important insights into the hormonal control of the hypothalamic-pituitary-gonadal axis (Pitteloud et al., 2008a, 2008b) as well as the molecular control of human puberty and reproduction (Balasubramanian et al., 2010; Bianco & Kaiser, 2009; Sykiotis, Pitteloud, Seminara, Kaiser, & Crowley, 2010). However, there are scant data on how the severe disruption of puberty impacts patients and how they cope with CHH. Indeed the 3 descriptive reports from the past 50 years (Bobrow et al., 1971; Huffer et al., 1964; Huisman et al., 1996) have included few patients (8, 13, and 8 respectively) and lacked validated measures. Two reports utilizing previously validated instruments focused exclusively on patient at the time of diagnosis (Aydogan et al, 2012; Lasaite et al., 2013). Therefore, this study contributes a nursing perspective to a gap in the literature that has direct relevance for developing interventions aimed at improving health outcomes and quality of life for these dispersed rare disease patients.

New application of the Health Promotion Model

This project, and the resulting manuscripts, point to possibilities for using Pender's HPM model for understanding medication adherence in chronic disease. Indeed, the only link between adherence and the HPM comes from a single report (case study) from 1997 that pointed to Pender's model as a possible framework for understanding adherence to anticonvulsant therapy among patients with epilepsy (Lannon, 1997). We demonstrate how the HPM can be used to dissect factors mediating medication adherence in chronic conditions and identifying targets for nursing sensitive interventions (Aims 1-4, see above Article n°2). Thus, the present study adds to the theoretical base of nursing practice by expanding the use of Pender's HPM.

The HPM has not previously been applied to rare disease patients - yet is has been put forth as a model for patient empowerment in diabetes (Ho et al., 2010). As delineated in the background, empowerment is a critical issue for rare disease communities (Ayme et al., 2008). Accordingly, these points suggested that the HPM could hold relevance for examining CHH men. Herein we provide supporting evidence that the HPM is indeed a useful middle-range theory that can be applied to a rare disease patient population - thus expanding applicability and adding to its theoretical robustness as a model for nursing. Future directions for this project will include drafting a manuscript focusing on the theoretical aspects of the HPM and novel applications for nursing research.

Innovative partnerships to reach dispersed and isolated patients

Another contribution of this thesis is that it adds to the evolving ways in which nursing research engages with patients, families, and promotes action for improved health and wellness within communities. Patients with rare diseases such as CHH, face a variety of

challenges that place them in the realm of heath inequities (Holtzclaw Williams, 2011) and empowerment is a critical factor for such patients (Ayme et al., 2008). We recognized patient expertise and developed partnerships with key patient advocates/community leaders to engage them as stakeholders in the research process. Indeed, such a community based participatory framework has previously been useful for empowering patients to overcome health inequities (Wallerstein & Duran, 2006). These partnerships included these expert patients as true collaborators in the process who made integral contributions throughout: from planning and development, to recruitment and conduct, to discussion of results and implications for future directions. As such, it is an example of how community engagement can be used not only as a research approach but also as a nursing intervention enabling participants to surmount health inequities.

Using technology to extend the reach of nursing care

By definition, patients with rare diseases are dispersed. However, advances in information and communication technology now make it possible to reach such dispersed individuals. Further, rare disease patients, such as the CHH described herein are highly active internet users. This interconnectivity provides new opportunities for healthcare delivery to connect patients with specialists as well as for peer-to-peer support. Such patient expertise and communities of knowledge can be drawn upon for crowdsourcing solutions in managing and coping with rare conditions.

This study demonstrates how nursing can leverage technology to extend its reach. This is particularly relevant and timely as demographic changes are challenging nursing to meet patient needs in an evolving and increasingly complex healthcare delivery system (Institute of Medicine (IOM), 2101). Technology will likely become increasingly important for nursing to

meet the needs of ever-growing numbers of chronic disease patients in the face of nursing shortages. This may result in technology being employed to monitor and treat patients. As this "high-tech" trend continues, there is a need to maintain what has been a critical aspect of nursing since the era of Florence Nightingale, i.e. care. It will be increasingly important for nursing to identify ways to combine the high-tech with the "high-touch" that has been so closely connected with nursing's role.

This study serves as a proof of principle to demonstrate how partnerships with stakeholders (expert patients) and leveraging technology can be combined to reach a large cohort of widely dispersed rare disease patients. In this mixed methods study we collected survey information from a large cohort of CHH men using a high-tech approach while qualitative focus groups (held in concert with patient support meetings) contributed a high-touch element. This mixed-methods approach grew from an initial patient support meeting three years ago organized by patient advocate Mr. Neil Smith. The stories shared that afternoon and the resulting positive patient responses following the meeting was the seed from which this high tech-touch project grew. Importantly, beyond the scientific impact of any resulting publications, this project and the patient support meeting/patient focus groups have had significant impact on human capital of the participants.

> *Though I have a loving family I had spent 64 years of my life feeling depressed, confused, lonely, alone, isolated, and frequently in despair. In just a couple of hours at the meeting 3 years ago in London those feelings decreased. For the first time ever I was with a group of people with whom I felt normal and at ease, valued and respected. This has made a tremendous difference in my life and I am very grateful. I am indebted to you. Thank you.*

This project therefore supports the notion that nursing can take a leading role in developing innovative healthcare delivery models to bridge existing shortfalls in care. Future directions and application of these nursing research findings include developing tailored online (e-

health) interventions. These nursing interventions combined with peer-to-peer support will focus on patient empowerment and activating individuals for enhanced self-care and wellness.

Conclusion

This thesis demonstrates that partnerships with patient community leader and utilizing web-based recruitment and data collection was an effective means to reach a large audience of dispersed rare disease (CHH) patients. Such an approach introduces potential bias as not everyone has internet access, and indeed this approach appears to be enriched with well-educated men. Further, one must account for a response bias of more proactive and/or more severely affected patients and take into account that as the online survey was in English responses may reflect a cultural Anglophone bias. For example, in discussing the results with the community leaders one online group moderators reflected that from their experience, fertility is a more frequent concern among those from Latin cultures. Therefore, these study findings should be interpreted in light of these limitations and should not be viewed as universal truths that can be generalized to all men with CHH.

The validity of the study findings were strengthened by several factors. First, for the qualitative survey, healthcare literacy, illness perceptions, depressive symptoms and medication adherence were assessed using previously validated instruments. For some aspects of hypogonadism (such as sexual/intimate life) where no CHH-validated instrument exists (Langham et al., 2008), we developed our own questions. Importantly, involving expert patients and utilizing a mixed-methods approach both helped contribute to the external validity of the study findings. First we sought face validity via input from patient advocates, yet a full validation process was not performed. Secondly, survey findings were explored in

the context of the patient focus group discussions corroborating the survey findings. Thus, one may be reasonably confident in the validity of the results.

A critical aspect of the nursing research process is the translational step of applying research findings (Chesla, 2008). Barriers to implementation slow this process and impede the transfer of findings and their application to improve healthcare (Crowley & Gusella, 2009). The next steps for this project will focus on this translational process. First, as pointed to in article °1 and °2, there is a need for patients to have access to information about their condition, treatment options, anticipatory guidance regarding treatment and links to reach clinical experts as well as for peer-to-peer support. As part of an international network of clinical investigators, basic researchers, geneticists, bioinformaticians, clinicians, nurses and patient advocates (COST Action BM1105), launching such information on the Action website seems like a logical, practical, and achievable translational objective. Second, as described in article °1, developing a talking sheet for patients to discuss concerns with their healthcare provider is a tangible patient-centered nursing intervention promoting shared decision-making. Providing such information openly on web-based platforms in multiple languages will help overcome some of the implementation based roadblocks. Third, subsequent steps for practice include reaching out to nursing colleagues and sharing this approach as a means by which nursing, or even an individual nurse, can impact the health and wellness of a dispersed rare disease patient population.

Future research directions could include several follow up projects. First, it would be interesting to evaluate a similarly sized cohort of female CHH subjects to see how similar or differently results are across gender. Presumably altered puberty would affect males and females differently, yet this is hypothetical at this point and examining similar questions among female patients could point to specific gender-based needs. Second, I believe it will

be important to move beyond the descriptive aspects of the present study to develop an interventional study. Some have described nursing as a complex intervention (Richards & Borglin, 2011) and I envision a subsequent step would be to develop an interventional study for CHH patients that would draw upon expertise from complementary fields including nursing, psychology and medicine. More specifically, one could imagine delivering complex interventions such as online tailored cognitive behavioral therapy (CBT) interventions (Andersson, Ljotsson, & Weise, 2011) paired with professional and/or peer-to-peer support. Such online CBT interventions have proven effective for treating anxiety and depression (Andersson & Titov, 2014; Mayo-Wilson & Montgomery, 2013). Such complex, web-based interventions could hold promise for addressing the depressive symptoms, low self-esteem, and body image concerns in these dispersed CHH men.

These next steps and future directions in both the clinical and research domains underscore that nursing is not solely focused on alleviating illness and suffering but is also focused on the patient's reaction to illness. This holistic, patient-centered view is a central aspect of nursing's contribution to healthcare.

I believe that to meet the emerging healthcare challenges, nurses at all level must move beyond health education activities and work collaboratively in interdisciplinary teams to develop complex interventions for behavior change to promote enhanced health outcomes, wellness, and quality of life for patients.

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Appendix 1: Literature search for citations relating to GnRH deficiency

	TOTAL	REVIEW ARTICLES	ORIGINAL ARTICLE/ CASE REPORT	CLINICAL TRIALS
1. Kallmann syndrome	176	43	46	3
1 AND genetics	167	43	30	*
1 AND phenotype	65	20	12	1
1 AND treatment	51	7	17	2
2. idiopathic hypogonadotropic hypogonadism (NOT kallmann	202	37	24	9
2 AND genetics	149	37	14	*
2 AND phenotype	44	14	4	*
2 AND treatment	92	17	12	9
3. isolated GnRH deficiency	51	15	10	*
3 AND genetics	28	14	5	*
3 AND phenotype	19	10	2	*
3 AND treatment	5	3	1	*
4. congenital GnRH deificiency	36	12	11	1
4 AND genetics	23	9	6	*
4 AND phenotype	10	6	1	*
4 AND treatment	10	4	3	1
1 OR 2 OR 3 OR 4 (n=331) (past 10yrs, human, English language)	**TOTAL**	**NOT RELEVANT**	**RELEVANT**	
REVIEWS	97	80	17	
ORIGINAL ARTICLE/CASE REPORTS	82	20	46	
CLINICAL TRIALS	11	9	2	
SYSTEMATIC REVIEWS	4	4	*	
META-ANALYSIS	0	*	*	
ALL SEARCHES CONDUCTED WITH FILTERS: PAST 10 YEARS, HUMAN, ENGLISH LANGUAGE				

Appendix 2: Literature search for citations relating to GnRH deficiency and nursing

MeSH	KS	IHH	IGD	CGD
nursing	0	0	0	0
needs assessment	0	0	0	0
nursing intervention	0	0	0	0
patient centered	0	0	0	0
self care	0	0	0	0
adherence	0	0	0	0
medication adherence	0	0	0	0
patient compliance	0	0	0	1*
quality of life	0	1*	0	0
attitude to health	0	1 *	0	0

KS = Kallmann syndrome
IHH =idiopathic hypogonadotropic hypogonadism
IGD = isolated GnRH deficiency
CGD = congenital GnRH deficiency
* unrelated

1st Search Modification: Search was expanded to include the more general term "hypogonadotorpic hypogonadism"

Notes: vast majority of articles identified related to age-related hypogonadism

MeSH	hypogonadotropic hypogonadism	Relevance	Notes
nursing (major or sub)	17	*	
needs assessment	9	*	
nursing intervention	0	*	
patient centered	1	*	
self care	11	1	1 original article on psychological aspects of Klinefelter syndrome
adherence	8	*	
medication adherence	1	*	
patient compliance	20	2	2 review articles on androgen therapy
quality of life	176	2	1 original article on Klinefleter syndrome, 1 on effects of testsoterone Tx on men with CHH
attitude to health	39	2	orignal articles - repeats of above
	282		

2nd Search Modification: Search was expanded to include the more general term "rare disease"

Notes: vast majority of articles identified were either case reports or disease specific reviews

MeSH	rare disease	Relevance	Notes
nursing (major or sub)	98	4	related to specific diseases, comprehensive care, policy, and discrimination
needs assessment	15	3	orphan drug policy, reginal care for rare diseases
nursing intervention	5	*	
patient centered	6	2	comprehensive multidisciplinary care, case management model for chronic/rare disease
self care	24	3	internet & empowerment
adherence	7	*	
medication adherence	3	*	
patient compliance	5	1	case management model for chronic/rare disease - repeat of above
quality of life	81	2	systematic review of QoL & health disparities
attitude to health	53	3	patient experience, physician interactions, operational innovations related to rare diseases
	297		

3rd Search Modification: Search was expanded to include the more general term "endocrine system disease"

Notes: vast majority of articles related to either cancer or diabetes (i.e. 'nursing' yielded >1,500 hits prior to adding addtional filters)

MeSH	endocrine system diseases	Relevance	Notes
nursing (major or sub)	218*	4	chronic care & planned visits
needs assessment	157	3	reviews of delayed puberty, health disparities
nursing intervention	36	1	Nursing in chronic care
patient centered	41	4	reviews on patient centered care, chronic care
self care	232	6	chronic care, self management
adherence #	105 #	2	medication side effects and adherence
medication adherence	33	*	
patient compliance	119 #	2	medication side effects and adherence (repeats)
quality of life	403*	5	psychological aspects, expert patients, 1 report on lack of QoL measures for CGD
attitude to health	232 #	3	health related behavior for specific diseases

ALL SEARCHES CONDUCTED WITH FILTERS: PAST 10 YEARS, HUMAN, ENGLISH LANGUAGE
* denotes additional filters: NOT diabetes mellitus, NOT tumor, NOT cancer, NOT surgery, NOT female
# denotes additional filters: NOT diabetes mellitus, NOT cancer, NOT surgery, male

Appendix 3: Questions relating to demographics and past experiences with healthcare

Please answer the following questions about yourself:

1. Gender: □ Male □ Female

2. Age: ____ years

3. Highest level of education:

□ elementary □ high school/vocational □ university □ post-graduate

4. How confident are you filling out medical forms by yourself?

□ extremely □ quite a bit □ somewhat □ a little bit □ not at all

5. Employment:

□ student □ working part-time □ working full-time □ retired □ unemployed

6. Type of employment: _____

7. Religion:_____ □ none

8. What is your relationship status?

□ single □ in a relationship □ married □ divorced

9. Do you have children?

□ no □ yes, biologic children □ yes, adopted children

Appendix 4: Questions relating to experiences with healthcare

We would like to know a little about when you were diagnosed with hypogonadotropic hypogonadism or Kallmann syndrome (we will call this CHH for congenital hypogonadotropic hypogonadism) and your past experiences with the healthcare system. Please answer the following questions:

1. How old were you when you were diagnosed with CHH? _____ years

2. Is there anyone else with CHH in your family?
□ No □ Yes If yes, how are they related to you?_____

3. How old were you when you started treatment (i.e. testosterone or gonadotropin/fertility injections)
to induce puberty? _____ years

4. What treatments have you had for this (please check all that apply)?
□ none □ testosterone (injections, patches or gel)
□ other _____ □ gonadotropin/fertility injections

5. Have you ever had a consultation or received treatment at an academic health center (such as a teaching hospital or research center)? □ No □ Yes

6. Have you ever had genetic testing? □ No □ Yes

7. Have you ever had genetic counseling? □ No □ Yes

8. Where have you searched for information to learn about CHH? (check all that apply)

□ internet (i.e. Wikipedia) □ online community (social media/chat)

□ family/friends □ medical literature

□ healthcare professionals □ Other:_____

9. From your experience, please rate the 3 most important sources:

__ internet (i.e. widkipedia)

__ medical literature

__ online community (social media/chat)

__ healthcare professionals

__ family/friends

__ other:_____

10.Within the healthcare system, have you ever experienced discrimination because of CHH? □No □ Yes

11. Is there a healthcare provider (i.e. doctor or nurse) who you feel really understands the medical aspects of your CHH? □ No □Yes

12. Is there a healthcare provider (i.e. doctor or nurse) who you feel understands your feelings about having CHH? □ No □ Yes

13. Have you ever sought professional counseling or therapy for issues related to CHH?

□ No □ Yes

14. Has a healthcare provider (either general practitioner or specialist) ever offered you counseling or a referral for professional counseling? □ No □ Yes

Appendix 5: Illness Perception Questionnaire- Revised

We are interested in your personal views about CHH. Please indicate how much you agree or disagree with the following statements about CHH.

		strongly disagree	disagree	neither agree nor disagree	agree	strongly agree
IP1	My CHH will last a short time	☐	☐	☐	☐	☐
IP2	My CHH is likely to be permanent rather than temporary	☐	☐	☐	☐	☐
IP3	My CHH will last for a long time	☐	☐	☐	☐	☐
IP4	My CHH will pass quickly	☐	☐	☐	☐	☐
IP5	I expect to have CHH for the rest of my life	☐	☐	☐	☐	☐
IP6	CHH is a serious condition	☐	☐	☐	☐	☐
IP7	CHH has major consequences on my life	☐	☐	☐	☐	☐
IP8	CHH does not have much effect on my life	☐	☐	☐	☐	☐
IP9	My CHH strongly affects the way others see me	☐	☐	☐	☐	☐
IP10	My CHH has serious financial consequences	☐	☐	☐	☐	☐
IP11	My CHH causes difficulties for those who are close to me	☐	☐	☐	☐	☐
IP12	There is a lot that I can do to control my symptoms	☐	☐	☐	☐	☐
IP13	What I do can determine if my CHH gets better or worse	☐	☐	☐	☐	☐
IP14	The course of my CHH depends on me	☐	☐	☐	☐	☐
IP15	Nothing I do will affect my illness	☐	☐	☐	☐	☐
IP16	I have the power to affect my CHH	☐	☐	☐	☐	☐
IP17	My actions will have no effect on the outcome of my CHH	☐	☐	☐	☐	☐
IP18	My CHH will improve with time	☐	☐	☐	☐	☐
IP19	There is little that can be done to improve my CHH	☐	☐	☐	☐	☐
IP20	My treatment will be effective in curing my CHH	☐	☐	☐	☐	☐
IP21	The negative effects of CHH can be prevented/avoided by my treatment	☐	☐	☐	☐	☐
IP22	My treatment can control my illness	☐	☐	☐	☐	☐
IP23	There is nothing which can help my condition	☐	☐	☐	☐	☐
IP24	The symptoms of my CHH are puzzling to me	☐	☐	☐	☐	☐

		strongly disagree	disagree	neither agree nor disagree	agree	strongly agree
IP25	My CHH is a mystery to me	☐	☐	☐	☐	☐
IP26	I don't understand my CHH	☐	☐	☐	☐	☐
IP27	My CHH doesn't make any sense to me	☐	☐	☐	☐	☐
IP28	I have a clear picture/understanding of my CHH	☐	☐	☐	☐	☐
IP29	My CHH symptoms change a great deal from day to day	☐	☐	☐	☐	☐
IP30	My symptoms come and go in cycles	☐	☐	☐	☐	☐
IP31	My CHH is very unpredictable	☐	☐	☐	☐	☐
IP32	I go through cycles in which my CHH gets better and worse	☐	☐	☐	☐	☐
IP33	I get depressed when I think about my CHH	☐	☐	☐	☐	☐
IP34	When I think about my CHH I get upset	☐	☐	☐	☐	☐
IP35	My CHH makes me angry	☐	☐	☐	☐	☐
IP36	My CHH does not worry me	☐	☐	☐	☐	☐
IP37	Having CHH makes me feel anxious	☐	☐	☐	☐	☐
IP38	My CHH makes me feel afraid	☐	☐	☐	☐	☐

Appendix 6: Questions regarding body image and sexuality

We would like to ask you a few questions to better understand how your CHH has affected your body image and your sexuality. This confidential information will help us better understand how we can help patients in these parts of their lives. If you are uncomfortable answering these questions you may skip to the next section.

1. Are you, or have you ever been concerned, embarrassed or ashamed of your body?
(i.e. avoiding situations that involve undressing in public places such as the gym or beach)

□ No □ Yes □ prefer not to respond

2. Have you ever been teased or ridiculed because of CHH?

□ No □ Yes □ prefer not to respond

3. Are intimate relationships difficult because of CHH?

□ No □ Yes □ prefer not to respond

4. Have you ever been sexually active?

□ No □ Yes □ prefer not to respond

Appendix 7: Questions regarding adherence (Morisky Medication Adherence Scale)

Many people have difficulty taking their medication. We are interested in your experiences. There is no right or wrong answer. Please answer each question based on your personal experience with your medication for CHH.

1. Do you sometimes forget to take your CHH medication? NO □ YES □

2. People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any times when you did not take your CHH medicine? NO □ YES □

3. Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it? NO □ YES □

4. When you travel or leave home, do you sometimes forget to bring along your CHH medication? NO □ YES □

5. Did you take your CHH medicine yesterday (or the last time you were due to take it)?
NO □ YES □

6. When you feel like your CHH is under control, do you sometimes stop taking your medicine? NO □ YES □

7. Taking medication is a real inconvenience for some people. Do you ever feel hassled about sticking to your CHH treatment plan? NO □ YES □

8. How often do you have difficulty remembering to take all your medications?
□ Never/Rarely □Once in a while □ Sometimes □ Usually □ All the time

9. Please estimate the longest period of time that you have gone without medical care (not under the care of a doctor or healthcare provider for your CHH):
_____ □ months □ years

10. Please estimate the longest period of time that you have been off your CHH medication (not at the instruction of your doctor or healthcare provider):
_____ □ months □ years

Appendix 8: Questions regarding depressive symptoms (Zung Self-Rating Depressive Scale)

For each item please choose the response that best describes how often you felt of behaved this way during the past several days.

	A little of the time	Some of the time	Good part of the time	Most of the time
1. I feel down-hearted and blue.	□	□	□	□
2. Morning is when I feel best.	□	□	□	□
3. I have crying spells or feel like it.	□	□	□	□
4. I have trouble sleeping at night.	□	□	□	□
5. I eat as much as I used to.	□	□	□	□
6. I still enjoy sex.	□	□	□	□
7. I notice that I am losing weight.	□	□	□	□
8. I have trouble with constipations.	□	□	□	□
9. My heart beats faster than usual.	□	□	□	□
10. I get tired for no reason.	□	□	□	□
11. My mind is as clear as it used to be.	□	□	□	□
12. I find it easy to do the things I used to do.	□	□	□	□
13. I am restless and can't keep still.	□	□	□	□
14. I am hopeful for the future.	□	□	□	□
15. I am more irritable than usual.	□	□	□	□
16. I find it easy to make decisions.	□	□	□	□
17. I feel that I am useful and needed.	□	□	□	□
18. My life is pretty full.	□	□	□	□
19. I feel that others would be better off if I were dead.	□	□	□	□
20. I still enjoy the things I used to do.	□	□	□	□

Appendix 9: Questions for patient focus group discussions

The online survey and discussions with patient community leaders identified 3 main areas that were explored during focus group discussions within the construct of the Pender HPM:

1. Challenges of living with CHH and aspects of coping and support:

- What has been the most difficult part of living with CHH? Are there positive aspects to having CHH?
- How has CHH impacted your life? What helps you cope with having CHH?
- Who do you get support form for dealing with your CHH? Do you find it difficult to talk to people about CHH? Who have you told about your CHH?
- What words of advice and encouragement would you give to a young man who has just found out he has CHH? What do you wish someone would have told you?

2. Impact of CHH on intimate and sexual life:

- How has CHH affected your sex life and intimate relationships?

3. Aspects related to adherence to treatment:

- CHH is a chronic condition and it is often hard to stick with treatment and keep appointments over time. Have you had periods when you were off treatment?
- How do you feel when you are on/off treatment?
- What do you think are the 3 most important things you need to do for your health related to CHH? What things prevent you from doing those things?
- What do you think the benefits are to you in treating your CHH?
- What are the things that keep you from sticking with your medication? What are the things which help you staying on treatment?
- Do you feel in control of your CHH medication? Do you administer your own CHH medication? Would you like to? Are there things that prevent you from self-administering your CHH medication?

Appendix 10: Confirmation of Publication - *Orphanet Journal of Rare Diseases*

Your article has been published in final version in Orphanet Journal of Rare Diseases

BioMed Central [post-publication@biomedcentral.com]
Envoyé : mardi 17 juin 2014 07:20
À : Dwyer Andrew

MS: 1717878705124747
Title: Identifying the unmet health needs of patients with congenital hypogonadotropic hypogonadism using a web-based needs assessment: implications for online interventions and peer-to-peer support
Authors: Dwyer A Andrew, Quinton Richard, Morin Diane, Pitteloud Nelly,
Journal: Orphanet Journal of Rare Diseases

Dear Mr Andrew DWYER,

We are delighted to confirm that your article is now available in final version format in Orphanet Journal of Rare Diseases, with the following citation:

Orphanet Journal of Rare Diseases.2014, 9:83
DOI: 10.1186/1750-1172-9-83

URL: http://www.ojrd.com/content/9/1/83

Do you want to promote your article and spread the word about your research?
You can share your article with colleagues quickly and easily from the article page:
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Best wishes,
The BioMed Central Production Team

email: post-publication@biomedcentral.com
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Appendix 11: Submission Confirmation (article 2)

A manuscript number has been assigned to Adherence to treatment, depressive symptoms and affective illness representations in men with congenital hypogonadotropic hypogonadism (JC-14-2052)

em.jcem.0.3a72b0.0f8c0254@editorialmanager.com de la part de JCEM [jcem@endo-society.org]
Envoyé : lundi 14 avril 2014 16:17
À : Dwyer Andrew

Dear Dr. Dwyer,

Your submission entitled "Adherence to treatment, depressive symptoms and affective illness representations in men with congenital hypogonadotropic hypogonadism" has been been assigned the following manuscript number: JC-14-2052.

You will be able to check on the progress of your paper by logging on to Editorial Manager as an author.
The URL is http://jcem.edmgr.com/.

Thank you for submitting your work to this journal.

Kind regards,

Kimberly Rosenfield, Staff Editor
Staff Editor
The Journal of Clinical Endocrinology & Metabolism

Appendix 12: Submission Confirmation (article 3)

Journal of Sexual Medicine - Manuscript ID JSM-04-2014-221
onbehalfof+jsm+issm.info@manuscriptcentral.com de la part de jsm@issm.info
Envoyé : lundi 14 avril 2014 12:56
À : Dwyer Andrew
Pièces jointes : Attached standard file: * ~1.pdf (29 Ko) ; Attached standard file: * ~2.pdf (203 Ko)

14-Apr-2014

Dear Mr. Dwyer:

Your manuscript entitled "Psychosexual development in men with congenital hypogonadotropic hypogonadism on long-term treatment: A mixed-methods study" has been successfully submitted online and is presently being given full consideration for publication in the Journal of Sexual Medicine.

Your manuscript ID is JSM-04-2014-221.

Please mention the above manuscript ID in all future correspondence or when calling the office for questions. If there are any changes in your street address or e-mail address, please log in to Manuscript Central at http://mc.manuscriptcentral.com/jsm and edit your user information as appropriate.

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Thank you for submitting your manuscript to the Journal of Sexual Medicine.

Sincerely,
Irwin Goldstein, MD
Editor-in-Chief
Journal of Sexual Medicine