

ONGOING RESEARCH

Rationale, design and methods of the ESPRIT study: Energy, Sexual desire and body ProPoRtions wIth AndroGel[®], Testosterone 1% gel therapy, in hypogonadal men

HERMANN M. BEHRE¹, LOTHAR HEINEMANN², ALVARO MORALES³, & CLAIRE PEXMAN-FIETH⁴

¹Centre of Reproductive Medicine and Andrology, University Hospital Halle, Germany, ²Centre for Epidemiology & Health Research, Berlin, Germany, ³Centre for Applied Urological Research, General Hospital and Queen's University, Kingston, Ontario, Canada, and ⁴Solvay Pharmaceuticals GmbH, Hannover, Germany

This manuscript is a 'work in progress' and has not been peer-reviewed.

Abstract

Hypogonadism is associated with a range of disease states that have significant effects on morbidity and mortality, and also affect quality of life. The ESPRIT study (Energy, Sexual desire and body ProPoRtions wIth AndroGel[®], Testosterone 1% gel therapy) is a 6-month, multinational, open label, observational study in hypogonadal men being treated with transdermal AndroGel[®] in usual daily clinical practice; 1,700–2,400 patients will be enrolled in Canada, Germany, Central and Eastern Europe, Russia and the Middle East. The main objective will be to evaluate the effect of AndroGel[®] on symptoms of hypogonadism and quality of life as assessed by the Aging Males' Symptoms scale. Further objectives include evaluating the effect and time to onset of improvement in erectile dysfunction and libido/sexual desire (International Index of Erectile Function), fatigue (Multi-dimensional Fatigue Index) and body composition (waist circumference, body mass index). Subgroup analyses will be performed: <50 years versus ≥50 years; absence versus presence of metabolic syndrome. The safety of AndroGel[®] will also be assessed. The study population will consist of newly diagnosed hypogonadal men (age ≥18 years), in whom testosterone deficiency has been confirmed by clinical features and biochemical tests according to international guidelines, who are currently being prescribed AndroGel[®] (testosterone 1% gel, starting dose 50 mg testosterone per day).

Keywords: *Body composition, energy, erectile dysfunction, fatigue, hypogonadism, quality of life, sexual desire, testosterone*

Introduction

Hypogonadism is a relatively common condition; the recent Hypogonadism in Males (HIM) study reported a prevalence of 38.7% in men aged 45 years or older who were attending primary care practices in the United States when hypogonadism was defined as a single morning total testosterone below 10.4 nmol/L (300 ng/dL) or on current testosterone therapy [1]. The prevalence was 25.5% when one or more hypogonadal symptoms were present in addition to a low testosterone level.

Hypogonadism is associated with a wide range of problems including reduced libido, erectile dysfunction, fatigue, depression, changes in body composition, metabolic syndrome and, in severe long standing cases, osteoporosis, many of which can markedly affect quality of life [2]. In addition, hypogonadism has been associated with a range of disease states that have significant effects on morbidity and mortality.

Metabolic syndrome has been shown to be associated with hypogonadism in observational data [3–5]. Low total testosterone and sex-hormone binding globulin, as well as clinical androgen deficiency, were all shown to be associated with an increased risk of developing metabolic syndrome in the Massachusetts Male Aging Study [5]. In addition, individual components of the metabolic syndrome such as hypertension, hyperlipidaemia, diabetes and obesity, are more prevalent among hypogonadal men. In the HIM study [1], for example, the odds ratios for having hypogonadism were 1.47 in men with hyperlipidaemia, 1.84 in those with hypertension, 2.09 with diabetes and 2.38 with obesity. There is also now clear evidence of a relationship between metabolic syndrome and cardiovascular morbidity and mortality [6–8]. The Kuopio Ischaemic Heart Disease Risk Factor Study, conducted in 1,209 Finnish men aged 42–60 years, found that men with metabolic syndrome were 3–4 times more likely to die of coronary heart disease [7].

Testosterone replacement therapy is indicated in men with confirmed low serum testosterone concentrations and symptoms of hypogonadism. Although there is no generally accepted lower limit for normal testosterone levels, the International Society of Andrology (ISA), International Society for the Study of the Aging Male (ISSAM) and European Association of Urology (EAU) guidelines recommend that levels above a threshold of 12 nmol/L (346 ng/dL) are normal, whilst levels below 8 nmol/L (231 ng/dL) represent hypogonadism [9,10]. Since symptoms of testosterone deficiency become manifest between 12 and 8 nmol/L, trials of treatment can be considered in those in whom alternative causes of these symptoms have been excluded [9]. The United States guidelines from the Endocrine Society suggest that testosterone replacement therapy may be indicated when testosterone levels are below the lower reference limit of the normal range for healthy young men that has been established in the laboratory performing the analyses [11]. In some laboratories, this is 10.4 nmol/L (300 ng/dL).

AndroGel[®] is a gel containing 1% testosterone that provides continuous transdermal delivery of testosterone for 24 hours following a single topical application. Daily changes in testosterone levels are of a similar amplitude to those observed during the circadian rhythm of endogenous testosterone [12]. It delivers physiological amounts of testosterone, with a 5 g dose (50 mg testosterone) resulting in an average increase in plasma testosterone of around 8.7 nmol/L (250 ng/dL) [12]. A large multicentre, 6-month, randomised, controlled trial in 227 hypogonadal men aged 19–68 years showed that AndroGel[®] (151 subjects) returned blood total testosterone levels to the normal range, which then also improved sexual function, as assessed by patient questionnaires, with beneficial changes in sexual motivation, sexual performance, sexual desire, sexual enjoyment, satisfaction with erection and percentage of full erection achieved [13]. As might be expected, this was accompanied by improvements in mood parameters. Other beneficial effects included an increase in lean body mass and muscle strength, as well as reductions in fat mass and percentage body fat.

Regardless of the type of testosterone therapy chosen, the ISA/ISSAM/EAU recommendations and the US Endocrine Society Guideline advocate monitoring during treatment to include a digital rectal examination (DRE) and determination of serum prostate specific antigen (PSA) at baseline in men more than 45 years old, with repeat measurements at 3 months and then annually thereafter [9–11]. Furthermore, the ISA/ISSAM/EAU recommends that the DRE and PSA be performed at quarterly intervals during the first year. A periodic haematological assessment is also advised.

It is the aim of this paper to describe the rationale, design and methods of a new, large, multinational study in the field of testosterone treatment – the ESPRIT study (Energy, Sexual desire and body PropoRtions wIth AndroGel[®], Testosterone 1% gel therapy).

Study objectives

The main objective of the ESPRIT study will be to evaluate the effect of AndroGel[®] on the symptoms of hypogonadism and quality of life, as assessed by the Aging Males' Symptoms (AMS) scale, after 6 months of therapy under usual daily clinical practice. Further objectives of the ESPRIT study will be to evaluate the effect and time to onset of improvement in the following hypogonadal symptoms: erectile dysfunction and libido/sexual desire as assessed by the International Index of Erectile Function (IIEF), fatigue as assessed by the Multi-dimensional Fatigue Index (MFI), and body composition (body mass index and waist circumference); the safety of AndroGel[®] will also be assessed. In addition, a number of subgroup analyses will be performed to compare men aged <50 years with those aged ≥50 years, those with and without a diagnosis of metabolic syndrome, and for each specific participating country.

Methods

Study design

The ESPRIT study is a 6-month, multicentre, multinational, non-interventional, observational study in hypogonadal men being treated with AndroGel[®] in a usual daily clinical practice, as opposed to a formal clinical trial environment. Data will only be recorded on patients for whom AndroGel[®] has already been chosen by the participating physician, independently from this study, and from assessments that are performed during standard patient care, rather than those that are predetermined and assigned as is customary in a controlled clinical study setting. The study will be conducted in Canada, Germany, Central and Eastern Europe, Russia and the Middle East, and it is planned that between 1,700 and 2,400 patients will be recruited by 575 to 800 physicians (urologists, endocrinologists and general practitioners) who have a particular interest in testosterone therapy. Each participating physician will be asked to collect data for at least three patients.

Study population

The study population will consist of newly diagnosed hypogonadal men not previously treated with a testosterone preparation, in whom testosterone deficiency has been confirmed by both clinical features and biochemical tests. The inclusion criteria are shown in Table I.

Treatment

The patients will receive transdermal AndroGel[®] (testosterone 1% gel) at a starting dose of 50 mg

Table I. Inclusion criteria for the ESPRIT study.

-
- Male subjects
 - Age ≥ 18 years
 - Newly diagnosed hypogonadal patients not previously treated with a testosterone preparation.
 - Hypogonadism whereby testosterone deficiency has been confirmed by both clinical features and biochemical tests.
 - Currently being prescribed AndroGel[®] according to the local Summary of Product Characteristics.
-

testosterone per day. The effects of treatment will be assessed over a 6 month period.

If serum testosterone levels are to be determined during the course of normal monitoring, the physician will instruct the patient to apply the gel to the shoulders, chest or upper abdomen, but not to the arms, on the day before the blood sample is due to be taken, in order to avoid contamination by the presence of residual gel. If possible, on the day of blood sampling, the patient will be asked to apply that day's gel only after the specimen has been taken.

Outcome measures

The AMS is a reliable, validated, self-administered, health-related quality of life scale designed to assess the symptoms of aging in males, to evaluate the severity of complaints/quality of life over time, and to measure changes pre- and post-androgen therapy [14–17]. The scale was originally developed in response to a lack of specific measures of the severity of aging symptoms and their impact on health-related quality of life in men. It consists of psychological, somatic and sexual sub-scales, is easy and fast to complete, and has good sensitivity and specificity. Moreover, the availability of the AMS in almost 30 languages is vitally important for international studies such as the ESPRIT [18,19]. The AMS scale has been used in numerous other studies of testosterone replacement therapy [18,20]. For example, it was used recently in an open study to assess the effects of 3 months' treatment with testosterone gel in 1,670 androgen-deficient men [18]. The AMS was able to measure the effects of treatment across the entire range of symptom severity, with those having little or no symptoms before treatment improving by 9%, whilst those with mild, moderate or severe symptoms improved by 24%, 32% and 39%, respectively. It was also able to predict the physician's subjective opinion about the treatment effects, showing specificity and sensitivity of more than 70%. Similar findings were reported in another post-marketing study conducted in 1,174 men treated with testosterone enanthate [20].

The IIEF is a 15-item self-administered scale that consists of five domains (erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction) [21,22]. It has been validated in

more than 30 languages and used as a primary endpoint in numerous clinical trials. Indeed, it is now recognised as the best available scale for evaluating erectile dysfunction and is the most well-known scale used by urologists. In the absence of a validated scale to evaluate libido in hypogonadal patients, the IIEF can be used to assess changes in sexual desire. In a recent study that was conducted to determine the relationship between sex hormones, physical complaints, depression, sexuality and life satisfaction in aging men, low IIEF sexual desire scores were related to low total testosterone levels [15]. Although the IIEF was originally developed as part of the clinical trial programme for sildenafil, it has been used in studies of testosterone replacement therapy [23,24]. Amongst these is a recent study in which the IIEF score was significantly increased after one month of treatment with AndroGel[®] whilst no changes were seen in the placebo group [23]. This improvement was paralleled by significant increases in total testosterone and free testosterone in the AndroGel[®] group.

The MFI is a validated 20-item self-administered scale to assess fatigue: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity [25]. Each of these five subscales contains four statements that are rated on a five-point scale ranging from 'yes, that is true' to 'no, that is not true'. In the previously discussed recent study that was conducted to determine the relationship between sex hormones, physical complaints, depression, sexuality and life satisfaction, lower total and free testosterone were found to be associated with reduced motivation on the MFI scale [15].

The criteria used to diagnose metabolic syndrome for the subgroup analyses will be the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (NCEP/ATP III) as modified recently by the American Heart Association (AHA)/National Heart, Lung and Blood Institute (NHLBI) in 2005 [26]. This definition is based on five commonly measured clinical criteria that have been shown to be associated with adverse cardiovascular outcomes: elevated waist circumference of ≥ 102 cm in non-Asian men or ≥ 90 cm in Asian men; elevated triglycerides (≥ 150 mg/dL or 1.7 mmol/L) or drug treatment for elevated triglycerides; reduced high-density lipoprotein (HDL) cholesterol (< 40 mg/dL or 1.03 mmol/L) or drug treatment for reduced HDL-cholesterol; elevated blood pressure (≥ 130 mmHg systolic or ≥ 85 mmHg diastolic) or drug treatment for hypertension; elevated fasting glucose (≥ 100 mg/dL or 6.1 mmol/L) or drug treatment for elevated glucose. Any three of these five criteria constitute a diagnosis of metabolic syndrome. This modified definition has the advantage of including a waist circumference value that is specific for Asian populations, as well as lower fasting blood glucose levels. The NCEP/ATP III criteria has

also been shown to be a better predictor of hypogonadism and impaired penile blood flow in men with erectile dysfunction than the International Diabetes Federation (IDF) criteria [27].

Assessments

The schedule of assessment visits will be in accordance with the local standard of practice and the treating physician's usual follow-up consultations. This will include a baseline/inclusion visit, one visit as close to 4 weeks after commencement of AndroGel[®] as possible, a further visit at 3 months and a final visit at 6 months as recommended by the prescribing information and international recommendations [9].

The assessments that will be performed at each visit are summarised in Table II. At the baseline visit, the patient's eligibility for the study will be verified by ensuring that they fulfil the inclusion and exclusion criteria. Evidence of testosterone deficiency will be determined by local laboratory tests as is usual in daily clinical practice and clinical features of hypogonadism. These will be documented using assessment scales (AMS, IIEF and MFI) in an objective manner. The patients will undergo a physical examination, including a DRE and measurement of height, weight, waist circumference, and sitting systolic and diastolic blood pressure. A medical

history will also be taken, with information on age, race, smoking habits, testicular abnormalities, prostate disease, diabetes and components of metabolic syndrome, and they will be asked about any medications they are currently taking including phosphodiesterase type 5 inhibitors, insulin, oral hypoglycaemics, and anti-hypertensive and lipid lowering drugs. At baseline and subsequent visits, monitoring parameters including PSA, haemoglobin and haematocrit, liver function and lipid levels will be recorded.

The clinical features of hypogonadism will be assessed at all subsequent visits, together with any changes in AndroGel[®] therapy or concomitant medications. The patients will be actively questioned by their physician regarding the occurrence of suspected adverse drug reactions (ADRs). These will be characterised according to their seriousness, severity and causal relationship to the study medication. Serious suspected ADRs will be reported as soon as possible to the Global Drug Safety and Surveillance Department of Solvay Pharmaceuticals, which will forward the reports to the regulatory authorities according to standardised procedures.

Study organisation, data collection and quality control

The study plan will be submitted to the Institutional Review Boards and/or Ethics committees and the

Table II. Schedule of proposed assessments and data capture.

Assessments	Visit			
	Baseline	4 weeks	3 months	6 months*
Eligibility	X	–	–	–
Clinical features of hypogonadism:				
AMS scale	X	–	–	X
IIEF scale	X	X	X	X
MFI scale	X	X	X	X
AndroGel [®] therapy changes		X	X	X
Medical history	X	–	–	–
Concomitant medications	X	X	X	X
Physical examination: weight, waist circumference, sitting systolic and diastolic pressure, digital rectal examination ^a	X	X ^b	X	X
Evidence of testosterone deficiency and monitoring parameters ^c :				
morning TT	X	X	X	X
morning or calculated FT	X	X	X	X
albumin	X	X	X	X
SHBG	X	X	X	X
PSA	X	–	X	X
haemoglobin	X	–	X	X
haematocrit	X	–	X	X
lipids	X	–	–	X
liver function tests	X	–	–	X
Next visit date	X	X	X	–
Adverse drug reactions	–	X	X	X
Overall study assessment	–	–	–	X

*or at time of premature termination; ^aheight also measured at baseline; ^bsitting systolic and diastolic pressure only; ^cresults recorded if test is performed by prescribing physician; AMS: Aging Males' Symptoms; IIEF: International Index of Erectile Function; MFI: Multi-dimensional Fatigue Index; TT: total testosterone; FT: free testosterone; SHBG: sex hormone binding globulin; PSA: prostate specific antigen.

study will be conducted in compliance with national legislation and the Declaration of Helsinki. An informed consent form approved by the relevant ethical committee will be completed by all participants, as required by local regulations for the conduct of observational studies. According to country-specific regulations, this study is described as either a post-marketing surveillance study, part of an educational programme or as a phase IV clinical trial. Implementation and monitoring of the study is the responsibility of local representatives of Solvay Pharmaceuticals. These personnel will be responsible for evaluating the progress of the study and ensuring that it is conducted in compliance with the approved protocol and applicable regulatory requirements. The investigators will allow the Solvay representatives direct access to the source documentation in order to verify the data reported in the case report forms. In addition, up to 5% of physicians will receive a monitoring visit by an external agency during which the completed case report forms will be compared to the patient files.

A co-ordinating centre is responsible for the preparation and distribution of materials, management of regulatory document collection, and review of edits and queries generated by data management and their resolution. Data capture, quality control, data management processes and statistical analyses are centralized in France.

Number of patients

The sample size was estimated based on a previous observational trial of hypogonadal men treated with intramuscular testosterone enanthate for 3 months, in which the mean (\pm standard deviation) improvement from baseline on the AMS scale was $31.8 \pm 18.1\%$ [28]. A sample size of 1,259 would be required for the two-sided 95% confidence interval (CI) for a single mean to extend 1% from the percentage change observed mean, assuming a standard deviation of 18.1%. As it is expected that data from about 25% of patients enrolled in observational post-marketing surveillance trials will not be evaluable, a total of 1,700 to 2,400 patients will be recruited.

Statistical analyses

The outcome parameters will be analysed for the intent-to-treat (ITT) population, i.e. all patients who received at least one dose of study treatment and for whom relevant values were available at baseline and at least one post-baseline visit. The last observation carried forward (LOCF) method will be used. The percentage change between baseline and post-baseline visits will be analysed using a paired-difference t-test and 95% confidence intervals will be calculated. The absolute changes between baseline and post-baseline visits will also be calculated.

The data will also be summarised by responder status. Responders will be defined as men who have had at least one documented total testosterone level within the normal range whilst receiving AndroGel[®]. In each of these categories, the following additional subgroups will be analysed: <50 years versus ≥ 50 years; absence versus presence of metabolic syndrome; country.

Safety will be analysed in all patients who received at least one dose of study medication. ADRs will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of suspected ADRs, and the number and percentage of patients who presented with suspected ADRs, will be summarised. Blood pressure, DRE and laboratory parameters will also be summarised.

Discussion

The ESPRIT study is the first large-scale international study to be conducted with AndroGel[®]; it will involve between 1,700 and 2,400 patients enrolled by several hundred physicians in Canada, Germany, Russia, Central and Eastern European and Middle Eastern countries. The study will be carried out in patients being treated in community clinical practices, as opposed to a formal clinical trial environment, and will therefore assess the effects of AndroGel[®] treatment under real life, everyday conditions. As it is an observational study, the decision to prescribe AndroGel[®] will be clearly separated from, and precede, the decision to include the patient in the study. Moreover, data will only be recorded from assessments that are performed as during the standard care for this type of patient.

At present, there is no clear data in the literature about when hypogonadal symptoms start to improve with testosterone replacement therapy, or the order in which they improve. This study will therefore evaluate the effect and time to onset of improvement in erectile dysfunction, libido/sexual desire, fatigue and body proportions. Such information is expected to be of major benefit in helping physicians to better manage patient expectations of treatment outcomes with regard to the timing of improvement of specific symptoms.

Subanalyses based on age and metabolic syndrome will also provide valuable information. Observational data suggest that metabolic syndrome is strongly associated with hypogonadism, and metabolic syndrome, in turn, is linked to increased cardiovascular morbidity and mortality. It will therefore be of interest to determine whether there are differences in the effects of testosterone replacement therapy between men with and without a diagnosis of metabolic syndrome.

In summary, the ESPRIT study represents the first large-scale international study to investigate the effects of AndroGel[®] on symptoms of hypogonadism and quality of life in hypogonadal men being

treated in everyday community clinical practice. It will also provide valuable information on the order in which hypogonadal symptoms improve, and subanalyses will allow assessment of the influence of age and metabolic syndrome on the response to treatment.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content of the paper. The authors acknowledge assistance from Jane Irons in the technical, linguistic and style editing of the manuscript.

References

- Mulligan T, Frick MF, Zuraw QC, et al. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. *Int J Clin Pract* 2006;60:762–769.
- Maggi M, Schulman C, Quinton R, Langham S, Uhl-Hichgraeber K. The burden of testosterone deficiency syndrome in adult men: economic and quality-of-life impact. *J Sex Med* 2007;4:1056–1069.
- Laaksonen DE, Niskanen L, Punnonen K, Nyysönen K, Tuomainen T-P, Valkonen V-P, Salonen R, Salonen JT. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. *Diabetes Care* 2004;27:1036–1041.
- Oh JY, Barrett-Connor E, Wedick NM, Wingard DL. Endogenous sex hormones and development of Type 2 diabetes in older men and women: The Rancho Bernardo study. *Diabetes Care* 2002;25:55–60.
- Kupelian V, Page ST, Araujo AB, Travison TG, Bremner WJ, McKinlay JB. J. Low sex hormone-binding globulin, total testosterone, and symptomatic androgen deficiency are associated with development of the metabolic syndrome in nonobese men. *Clin Endocrinol Metab* 2006;91:843–850.
- Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005;365:1415–1428.
- Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002;288:2709–2716.
- Isomaa B, Almgren P, Tuomi T, Forsén B, Lahti K, Nissén M, Taskinen M-R, Groop L. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001;24:683–689.
- Nieschlag E, Swerdloff R, Behre HM, Gooren LJ, Kaufman JM, Legros JJ, Lunenfeld B, Morley JE, Schulman C, Wang C, Weidner W, Wu FC. Investigation, treatment and monitoring of late-onset hypogonadism in males. *Aging Male* 2005;8:56–58.
- Lunenfeld B, Saad F, Hoese CE. ISA, ISSAM and EAU recommendations for the investigation, treatment and monitoring of late-onset hypogonadism in males: Scientific background and rationale. *Aging Male* 2005;8:59–74.
- The Endocrine Society. Testosterone therapy in adult men with androgen deficiency syndromes: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2006;91:1995–2010.
- Swerdloff RS, Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ, Weber T, Longstreth J, Berman N. Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men. *J Clin Endocrinol Metab* 2000;85:4500–4510.
- Wang C, Swerdloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G, Matsumoto AM, Weber T, Berman N, Testosterone Gel Study Group. Transdermal testosterone gel improves sexual function, mood, muscle strength and body composition in hypogonadal men. *J Clin Endocrinol Metab* 2000;85:2839–2853.
- Heinemann LA, Saad F, Heinemann K, Thai DM. Can results of the Aging Males' Symptoms (AMS) scale predict those of screening scales for androgen deficiency? *Aging Male* 2004;7:211–218.
- Beutel ME, Wiltink J, Hauck EW, Auch D, Behre HM, Brähler E, Weidner W, the Hypogonadism Investigator Group. Correlations between hormones, physical, and affective parameters in aging urologic outpatients. *Eur Urol* 2005;47:749–755.
- Heinemann LA. Aging Male's Symptoms scale: A standardized instrument for the practice. *J Endocrinol Invest* 2005;28(Suppl 11):34–38.
- Daig I, Heinemann LA, Kim S, Leungwattanakij S, Badia X, Myon E, Moore C, Saad F, Pothoff P, Thai DM. The Aging Males' Symptoms (AMS) scale: Review of its methodological characteristics. *Health Qual Life Outcomes* 2003;1:77.
- Heinemann LA, Moore C, Dinger JC, Stoehr D. Sensitivity as outcome measure of androgen replacement: The AMS scale. *Health Qual Life Outcomes* 2006;4:23.
- Heinemann LA, Saad F, Zimmermann T, Novak A, Myon E, Badia X, Pothoff P, T'Sjoen G, Pöllänen P, Goncharow NP, Kim S, Giroulet C. The Aging Males' Symptoms (AMS) scale: Update and compilation of international versions. *Health Qual Life Outcomes* 2003;1:15.
- Moore C, Huebler D, Zimmermann T, Heinemann LA, Saad F, Thai DM. The Aging Males' Symptoms scale (AMS) as outcome measure for treatment of androgen deficiency. *Eur Urol* 2004;46:80–87.
- Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The International Index of Erectile Function (IIEF): A multidimensional scale for assessment of erectile dysfunction. *Urology* 1997;49:822–830.
- Rosen RC, Cappelleri JC, Gendrano N. The International Index of Erectile Function (IIEF): A state-of-the-science review. *Int J Impot Res* 2002;14:226–244.
- Chiang HS, Hwang TI, Hsui YS, Lin YC, Chen HE, Chen GC, Liao CH. Transdermal testosterone gel increases serum testosterone levels in hypogonadal men in Taiwan with improvements in sexual function. *Int J Impot Res* 2007;19:411–417.
- Yassin AA, Saad F. Improvement of sexual function in men with late-onset hypogonadism treated with testosterone only. *J Sex Med* 2007;4:497–501.
- Smets EM, Garssen B, Bonke B, De Haes JC. The Multi-dimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 1995;39:315–325.
- Grundey SM, Cleeman JJ, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Spertus JA, Costa F, American Heart Association, National Heart, Lung and Blood Institute. Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung and Blood Institute scientific statement. *Circulation* 2005;112:2735–2752.
- Corona G, Mannucci E, Petrone L, Schulman C, Balercia G, Fisher AD, Chiarini V, Forti G, Maggi M. A comparison of NCEP-ATPIII and IDF metabolic syndrome definitions with relation to metabolic syndrome-associated sexual dysfunction. *J Sex Med* 2007;4:789–796.
- Moore C, Huebler D, Zimmermann T, Heinemann LA, Saad F, Thai DM. The Aging Males' Symptoms scale (AMS) as outcome measure for treatment of androgen deficiency. *Eur Urol* 2004;46:80–87.

Copyright of *Aging Male* is the property of Taylor & Francis Ltd and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.