

## Systematic Review

# Ageing: Postponing Morbidity

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### Article information

Received: August 17<sup>th</sup>, 2018; Revised: September 19<sup>th</sup>, 2018; Accepted: September 27<sup>th</sup>, 2018; Published: October 5<sup>th</sup>, 2018

### Cite this article

Wiseman R. Ageing: Postponing morbidity. *Epidemiol Open J.* 2018; 3(1): 1-6. doi: [10.17140/EPOJ-3-112](https://doi.org/10.17140/EPOJ-3-112)

## ABSTRACT

### Aim

To investigate whether the morbidities associated with ageing – loss of muscle mass with consequent weakness, increase in adipose-tissue mass, thinning of skin, loss of bone mineral density followed by increase in fracture rate, decreased energy, and reduction in bone marrow output – can be prevented or postponed by a combination of modern pharmaceutical agents.

### Methods

Electronic databases were scrutinized for the actions and side-effects of compounds which have known and specific effects.

### Results

Anabolic steroids, androgenic hormones and their precursors, as well as growth hormone and erythropoietin were assessed. The benefits of each of these, and their potential adverse effects, together with suggested doses at which they may be used in combination, are presented.

### Conclusions

The data indicate that there are many probable benefits to ageing individuals in postponing morbidity by the suggested combination of compounds, although no size effects can be determined without a large population study. It is likely that there would be a low-level of side-effects. However, before a population study, a clinical trial to test these assumptions is suggested. Apart from the specific benefit to individuals, if successful the combination would engender wide-spread usage with many important benefits to society, not least on the amount and cost of care-giving.

### Keywords

Ageing; Morbidity; Anabolic/Androgenic hormones; Growth hormone; Erythropoietin.

## INTRODUCTION

This article discusses the fact that the morbidities of ageing, including hormonal, metabolic, haemopoietic and immunological, can be postponed; and that the pharmacological means to do so are already available. This does not necessarily mean that death will be postponed, but it does mean that some or many of the disturbances to health and welfare in later years may be avoided – a situation that Fries has termed ‘compression of morbidity’.<sup>1</sup> Age changes are characterised by loss of molecular structure, and hence function, according to present hypothesis, which speculates that

the escalating loss of molecular fidelity ultimately exceeds repair and turnover capacity.<sup>2</sup>

Although life-styles play an important part in morbidity (at almost any age) – as well as age at death – presumably by preventing or delaying molecular disorder, it is quite possible that pharmaceutical intervention can also play a part by preventing or delaying the molecular fragmentation that is claimed to be an intrinsic part of ageing. Indeed, pharmaceutical intervention over the last century, in association with better sanitation to prevent many diseases, has done much to postpone morbidity and decrease

age-changes. Antibiotics, statins, chemotherapy are among many which have led to these improvements. Further pharmaceutical intervention along the lines suggested in this article may allow age changes to be further postponed.

If avoidance or postponement of chronic disease, debilitating and often ultimately fatal, is possible, and if implemented on a wide scale, this would result in large social and economic consequences for individuals, families, and society at large. In addition to the probable benefits of pharmaceutical intervention, laboratory models have demonstrated that every aspect of ageing can be manipulated, from DNA damage to cross-linking of connective tissue collagen and elastin, to lipids and brain amyloid levels.<sup>3</sup>

## METHODS

A systematic search was made through MEDLINE® and other electronic search engines of the uses, benefits and side effects of all pharmaceutical agents that were thought to be useful in postponing or amending the diseases and frailties of ageing. Further data on these agents was supplemented from textbooks, especially on Gerontology, references in publications, and standard medical reference books.

## POTENTIAL AGENTS

The factors which cause loss of health in later years include – but are not limited to – loss or diminution of anabolic steroids and sex hormones or their precursors with consequent loss of muscle mass; reduction in growth hormone secretion; reduction of erythropoietin secretion causing diminution of red cell production; depletion of immunological responses; possibly also reduction of collagen production; and neurological deterioration. Most of these factors have pharmacological remedies which if used in combination would prevent much ill-health. All the remedies or agents are potent products and have side-effects, thus the remedies given together may cause a multiplication of adverse effects, but in any event if given in combination should be prescribed in small doses. A further factor against the use of most of these products is that under current legislation (in many countries including the UK), prescription of them is illegal.

There are a number of known agents which would be of benefit. These are anabolic steroids, sex hormones or their precursor DHEA, erythropoietin and growth hormone.

### Anabolic Steroids/Androgenic Hormones and their Precursors (DHEA and DHEAS)

Although a few anabolic steroids or androgenic hormones possess pure androgenic activity or pure anabolic activity, most compounds exhibit both types with one or the other predominating.<sup>4</sup> The anabolic steroids were developed in order to increase protein-building in cachexia and wasting diseases but are much misused by athletes, body builders and sports persons to increase muscle mass and body weight. Androgenic steroids, including testosterone, dehydroepiandrosterone sulfate (DHEAS), dehydroepiandro-

sterone sulfate (DHEAS), and dihydrotestosterone (DHT) possess similar activity but have greater virilising and masculinising effects than anabolic steroids. However, all androgens retain some anabolic activity. In addition, androgenic steroids have other multiple effects – testosterone, for example, can be viewed as a pro-hormone, peripherally converted to 5 $\alpha$ -dihydrotestosterone (DHT) and 17 $\beta$ -oestradiol (E2).<sup>5</sup> DHT has greater affinity for androgen receptors than testosterone, hence it amplifies testosterone action.<sup>6</sup> Testosterone is absorbed from the gastrointestinal tract and undergoes first-pass hepatic metabolism when given orally. In order to avoid this, it needs to be given intra-muscularly, subcutaneously or transdermally.

**General effects:** Although the primary indication for testosterone is for the treatment of men with hypogonadism<sup>5,7,8</sup> where it improves sexual functioning and the full development of the sexual organs, many studies have shown that it has beneficial effects on bone, muscle, cardiovascular functions and brain. Testosterone has been shown to be beneficial in some studies of dementia,<sup>9</sup> on quality of life,<sup>10</sup> in heart failure,<sup>11,12</sup> as well as hormonal syndromes such as delayed puberty, erectile dysfunction and gender reassignment, as might be expected.

Experts from the Boston Group<sup>7</sup> recommended testosterone therapy for “*men with symptomatic androgen deficiency to induce and maintain secondary sex characteristics and to improve their sexual function, sense of well-being, muscle mass and strength, and bone mineral density*”, but recommended against “*testosterone therapy in patients with breast or prostate cancer, a palpable prostate nodule or indurations*”. They advised against offering it to “*all older men with low testosterone levels*” but confusingly suggested that it could be offered on an individual basis “*after explicit discussion of the uncertainty about the risks and benefits*”.

### Dehydroepiandrosterone (DHEA)

A precursor of testosterone and other sex hormones; it is produced by the adrenal gland and exists largely as a water-soluble sulphate (DHEAS). It is well established that there is a steep age-associated decline in circulating levels of DHEA and DHEAS.<sup>13</sup>

It has been reported (in double-blind placebo-controlled trials) that taking DHEA 50 mg nocte for three months leads to an increase in the serum concentration of DHEA, of androstenediol, testosterone and DHT in women, but only androstenediol in men,<sup>14</sup> it did not affect the amount of body fat or glucose metabolism, but both men and women felt a greater sense of ‘well-being’. There was no change in libido in either sex, and there were no side effects. Another similarly designed study<sup>15</sup> looked at changes in the lymphocytes after administering 50 mg DHEA each morning for three weeks and reported that the number and activity of natural killer cells (CD8<sup>+</sup>/CD56<sup>+</sup>) increased, as did insulin binding. Again, there were no adverse effects.

A further double-blind placebo-controlled<sup>16</sup> with DHEA in a dose of 100 mg per day for one year again showed an increase in insulin-like growth factor, but the higher dose led to an increase in lean body mass and (in men but not women), in muscle strength

at the knee, presumably due to increased force by the quadriceps. There was no change in libido, neither in men nor women.

Adverse effects of androgens<sup>4</sup> include retention of sodium and water with consequent oedema, hypercalcaemia, impaired glucose tolerance, increased low-density lipoprotein (LDL) cholesterol, decreased high-density lipoproteins (HDL) cholesterol, polycythaemia and decreased platelet count. Venous thromboembolism, including deep vein thrombosis (DVT) and pulmonary embolism, have been reported.

In men, large doses of testosterone may suppress spermatogenesis and testicular atrophy may follow. In elderly males, gynaecomastia and prostatic hyperplasia may occur.

### Prostatic Cancer

Although there is debate whether or not the incidence of prostatic cancer might theoretically be increased or not, careful reviews have concluded that prospective cohort studies have not shown support for the hypothesis that high-levels of circulating androgens are associated with increased risk of prostate cancer.<sup>17,18</sup> Indeed, high-grade prostate cancer has been associated with low plasma testosterone levels.<sup>17</sup>

In women, androgens as an adjunct to hormone replacement therapy are known to produce various signs of virilism.

Since androgens are strong stimulants or initiators of prostatic cancers, and anti-androgens such as cyproterone acetate are used in their treatment, the question of whether testosterone or DHEA promotes such tumours has been intensively studied.

For example, after a wide-ranging review of the existing literature, including placebo-controlled trials and adverse event reporting, Gould and Kirby<sup>18</sup> concluded that there was no apparent increase of prostatic cancer in hypogonadal men given testosterone, that there was no conclusive evidence that levels of circulating testosterone in men developing prostate cancer are higher than in controls; indeed, some studies showed that men with low levels are at greater risk. They also affirmed that testosterone treatment should be considered in those who need it, but it is important to exclude prostate cancer (by PSA test and rectal examination) before the initiation of treatment because although testosterone might promote pre-existing prostatic cancer, it is an open question whether or not it can induce it. Raynaud<sup>17</sup> in a small study also showed no increase in the risk of prostate cancer.

**Hepatotoxicity:** Abnormal liver function tests, cholestasis, jaundice and hepatic tumours may occur with both androgens and anabolic steroids, particularly with the 17 $\alpha$ -alkylated derivatives. Tumors have included hepatocellular carcinoma, benign adenomas and angiosarcomas. Prolonged treatment and high doses may be significant contributory factors, although regression occurs on withdrawal of the agent.<sup>19,20</sup>

**Cardiovascular effects:** The FDA, in reviewing the results<sup>21</sup> of a

number of placebo-controlled studies that were concerned with cardiovascular risk, decided on the basis of two further studies that demonstrated increased risk of stroke, heart attack and death in the testosterone-treated group, to issue a 'Safety Announcement'. However, the FDA stated that 'We have not concluded that FDA-approved testosterone treatment increases the risk of stroke, heart attack or death' perhaps because several but not all epidemiological studies reported an association of low testosterone levels with higher overall mortality or mortality from cardiovascular disease (CVD).<sup>22-25</sup> The FDA urged all parties to balance benefits against potential risks, and to report side-effects.

As for DHEA and DHEAS, Barrett-Connor and Goodman-Gruen<sup>26</sup> noted a striking linear decline of these androgens with age in a 19-year follow-up of their cohort of men and women aged 30-88 years, with DHEAS not being associated with cardiovascular disease (CVD) nor ischaemic heart disease, but there was a modestly (statistically significant) reduced risk of fatal CVD in men and a (non-statistically significant) increased risk of fatal CVD in women.

**General effects of DHEA:** Prescribing DHEA (as opposed to testosterone with all the difficulties of route of administration) to ageing men and women in doses of 50 mg and 100 mg orally in a 6-month placebo-controlled cross-over study<sup>13</sup> restored DHEA and DHEAS to levels found in young adults within two weeks of the start of administration, with no changes in insulin sensitivity, no lipid changes (except for a slight decline in HDL for women), improvement in immune factors, an absence of side effects and "a remarkable increase in perceived physical and psychological well-being for both men and women" but no change in libido for either gender.<sup>15</sup> An investigation<sup>13</sup> of 100 mg oral dose given nightly for one year, in a cross-over placebo-controlled design, showed significant changes in steroid levels, increases for both genders in IGF-I, increases in lean body mass, with knee-extension/flexion muscle strength increased in men but not in women. There were no changes in lipid profile or apolipoproteins, or insulin, or glucose levels. Fat body mass significantly decreased in men but not in women. A later study of postmenopausal women by the same Memphis group<sup>27</sup> showed increased T-lymphocyte binding, increased sex hormones, and declines in SHBG and serum triglycerides as compared to placebo but no changes in fasting HDL, neither LDL nor total cholesterol. The authors concluded that "a daily dose of 100 mg for 6-months appears to be excessive with respect to the increment of androgens in women and may induce undesirable effects with time". However, they commented that 50 mg per day of oral DHEA gave supra-physiologic androgen levels and considered that 25 mg per day may be more appropriate. There is insufficient data at present to pin-point the exact dose required, and the optimal dose may differ between men and women.

In commenting on this and other studies, an editorial in the Lancet<sup>28</sup> in 1995 stated "enough is known or suspected to warrant investigation of DHEA(S) as an effective, worthwhile, and relatively risk-free replacement therapy in old age", although one year later the British Medical Journal<sup>29</sup> was still doubtful, asserting that there was still not enough evidence to recommend routine treatment.

However, it is now generally considered that DHEA, if administered orally in a dose of 50 mg daily, will provide the androgenic and anabolic requirements without significant adverse effects.

### Growth Hormone

Diminished secretion of growth hormone with age is responsible, at least in part, for a number of features which characterize ageing – the decrease in lean body mass, the increase in adipose-tissue mass and the thinning of skin,<sup>30</sup> as well as decrease in quality of life<sup>31</sup> including social isolation.<sup>32</sup>

It has been noted that growth hormone replacement decreases fat mass,<sup>33</sup> particularly in the abdominal region, and increases lean body mass, as well as increasing markers of bone turnover and bone mineral density.<sup>34</sup> However, although growth hormone treatment in adults with growth hormone (GH) deficiency increases muscle mass, for instance in the quadriceps, there is apparently no increase in quadriceps force.<sup>35</sup> The increase in lean body mass in adult GH-deficient patients is due, it has been reported, to an increase in protein synthesis.<sup>36</sup> Replacement dose in adults (given to those with previous pituitary surgery or hypothalamic- pituitary irradiation) is 0.125 IU/kg/week for the first four weeks and 0.25 IU/kg/week thereafter; starting at the lower dose is thought to minimise side-effect incidence.<sup>33</sup> Most common side-effects were arthralgia and peripheral oedema.<sup>28</sup>

### Erythropoietin (EPO)

This is a glycoprotein, also known as haemopoietin, secreted by the kidney in response to cellular hypoxia. It stimulates red cell production in the bone marrow; low-levels are continually secreted to account for normal red blood cell turnover.

Recombinant EPO (rhEPO) was first successfully used in 1987 to correct anaemia.<sup>37</sup> It has been used in the treatment of anaemia from chronic kidney disease (especially for the anaemia of patients maintained on dialysis for end-stage renal disease),<sup>38</sup> and for anaemia associated with myelodysplasia, cancer chemotherapy, and inflammatory bowel disease.<sup>39</sup> Risks may include myocardial infarction, stroke, hypertension (prevented by dietary restriction of potassium<sup>39</sup>), epilepsy, allergic reactions and venous thromboembolism, although the incidence of adverse effects was not statistically different in one study of 116 patients between the EPO and non-EPO groups.<sup>38</sup> Risks increase if haemoglobin is raised above 11-12 g/dL.<sup>40</sup> Recombinant EPO has been and is used illicitly as a performance-enhancing drug.<sup>41</sup> Intolerance to subcutaneous injection has been reported.<sup>38</sup>

In the treatment of anaemia, the dose of the non-recombinant EPO is usually 75 to 450 units per kg body weight weekly, in three divided doses, given by injection.<sup>4</sup> The dose of rhEPO ('Epogen') in anaemia of chronic kidney disease is 50-100 units/kg intravenously three times weekly.<sup>40</sup>

If given for ageing with other agents, and not specifically

for anemia, a smaller dose would undoubtedly be sufficient; perhaps 25 units/kg once or twice weekly intravenously would suffice.

### CONCLUSIONS

The disturbances of ageing in the human body can be postponed or prevented by a combination of modern pharmacological agents which are currently available, although due to wide-spread misuse it is at present illegal to prescribe them. The doses suggested are on the basis of minimising the dose of that when given alone, since it is not known what the effects are of all three agents when given together; also, doses may differ between men and women, especially for the anabolic/androgenic moiety. It is suggested that clinical trials be instigated with the regime proposed. The compounds and doses are (i) oral DHEA, in a dose of 50 mg nightly; (ii) growth hormone, by injection with 0.0625 IU/kg/week for the first four weeks and 0.125 IU/kg/week thereafter (starting at the lower dose is thought to minimise side-effect incidence); and (iii) recombinant EPO by intravenous injection at a dose of 25 units/kg once or twice weekly.

The agents in this regime, which can be given to both ageing men and women, should increase lean muscle mass, decrease fat mass, have beneficial effects on bone, memory, cardiovascular health, improve blood sugar levels, have positive effects on mood, probably have no effect on libido, but will increase production of erythrocytes and as a consequence improve brain and lung function. There should be either no effect or a beneficial effect on lipid levels. In general, but with some exceptions, they should be free of adverse effects.

The uncertainty of possible side-effects of these products given in combination warrant a robust prospective clinical trial. No numeric data can be available until the results of such a trial (or trials) are available. A clinical trial would determine the benefits and adverse effects of this regime, although the amount of time that morbidity is postponed in any individual would of course be unknown. A large cohort study would be needed to determine the size effect in a population. If results show beneficial outcomes without serious adverse effects, then we are confident the pharmaceutical industry will quickly develop an enteral or dermatological means of EPO delivery, and if enteral then probably combine all the constituents in a single tablet or capsule.

Illicit use of these compounds might be expected; accordingly, some form of control of their use may be needed, but the fact that some persons may abuse their use, perhaps to gain unfair advantage in sport, should not prevent the benefits of use by the law-abiding majority.

The widespread use of these agents in combination will have an important effect on the amount of morbidity in the elderly and, aside from the benefit to the individual, should relieve to some extent the current pressures on the funding and numbers of care-giving. It will also be one further step in the change from medicines to treat diseases to medicines for prevention of diseases, in this case the morbidity of ageing.

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