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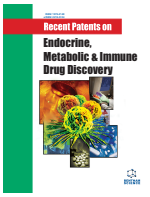
Serum Testosterone and Cognitive Function in Ageing Male: Updating the Evidence



Vito A. Giagulli*, Edoardo Guastamacchia, Brunella Licchelli and Vincenzo Triggiani

Interdisciplinary Department of Medicine-Section of Internal Medicine, Geriatrics, Endocrinology and Rare Diseases. University of Bari "A. Moro", Bari, Italy

Vito A. Giagulli

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Abstract: ***Background:*** Testosterone (T) deficit, either in prepubertal or postpubertal form of hypogonadism, seems to play a key role in impairing cognitive function, including memory, attention, language and visuospatial abilities, especially in elderly men.

Objective: Several studies have recently showed the association between low serum T levels and important cognitive dysfunctions in ageing male as well as in subjects suffering from Alzheimer's disease (AD), mild cognitive impairment (MCI) and even depression, suggesting that T could exert an active neuroprotective role.

Methods: By searching PubMed and recent patents (ranging from 2010 to 2015), we identified several observational and intervention studies dealing with T and cognitive function in adult and ageing men. Findings were reviewed, thoroughly examined and, finally, summarized herein.

Results: Although a large number of studies have been carried out so far, conclusive evidence cannot be drawn, in particular, for cognitive disorders in males. Conversely, T supplementation has been suggested for depressive syndrome in young and ageing men. To date, no clinical data have been carried out on cognitive dysfunctions employing the quoted patents in men.

Conclusions: Studies aiming to evaluate the role of serum T and its supplementation in adult and ageing men with T deficiency syndrome need to be encouraged, given that subjects affected by overt hypogonadism, either in prepubertal (i.e. Klinefelter syndrome) or postpubertal forms (chemical castration in subjects affected by prostate cancer), often complain of cognitive dysfunction, and seem to considerably benefit from T replacement therapy.

Keywords: Ageing male, Alzheimer's disease, cognitive dysfunction, depression, male hypogonadism, testosterone deficiency Syndrome.

INTRODUCTION

Cognitive performance, consisting in attention, memory, language and visuospatial abilities, declines as men grow older [1-3]. Given that in western countries elderly people are expected to be increasing in number in the next few years, the number of men affected by mild cognitive impairment (MCI) [4], dementia and Alzheimer's disease (AD) [5] is estimated to be rising too. In this context, it is not surprising that the cost of those patients' care is estimated over $ 180 billion per year in the United States [6].

Although the prevalence of cognitive dysfunctions may be different depending on the definition and methodology employed, it proves to be higher in adult-old men than in young ones. Indeed, moderate forms of memory impairment occur in about 13% of adults aged more than 65, while it can be diagnosed in more than 30% in men over 80. On the other hand, if memory impairment is defined according to the National Institute of Mental Health criteria, its prevalence turns out to be about 40% in individuals aged 60-80 [7]. However, 25% of men aged 68-78 have been found to suffer from "aging-associated cognitive decline" as defined by the International Psychogeriatric Association [8]. Finally, the prevalence of mild cognitive impairment (MCI) that is a transitional state between the normal ageing process and overt Alzheimer's disease (AD), can be estimated between 3 and 30% in men aged more than 75 [9].

It is generally accepted that several hormones may have an important role in brain organization and development and in sexual orientation during fetal life or in behavior, neuroprotection and cognitive functions in adult and aging subjects. A lot of research about the role of hormones in cognition has been undertaken, as well as several intervention studies have been carried out to evaluate the effect of the substitutive hormone therapy on those patients affected by cognitive loss. As a matter of fact, thyroid [10] glucocorticoid [11] and mineralcorticoid hormones [12] prove to affect brain functions in young and elderly men. However, in men

*Address correspondence to this author at the Interdisciplinary Department of Medicine Section of Internal Medicine, Geriatrics, Endocrinology and Rare Diseases. University of Bari "A. Moro" Piazza Giulio Cesare, 70123 Bari, Italy; Tel:/Fax: 00390804091368; E-mail vitogiagulli@alice.it

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sexual hormones and especially T seem to have a key role in modulating some brain functions such as those involved in sexual orientation, depression and cognitive abilities (especially learning, memory and spatial cognitions) [13].

The male ageing process is characterized by a gradual decline of testosterone (T) levels, as well as by a significant rise in serum levels of Sex hormone Binding Globulin (SHBG) [14] which, notwithstanding T metabolic clearance has been shown to be reduced in ageing men [15], brings about a steeper decrease in circulating free T (FT) than serum T [16]. This natural event may be worsened in the presence of diseases and comorbid conditions (i.e. obesity, metabolic diseases, renal failure, diabetes mellitus, etc.) and even medications that can often be prescribed for those diseases causing the exacerbation of the same ageing process. In addition, the serum T reduction can contribute to alterations in body composition (i.e. obesity) [17], diminution in energy, muscle strength, sexual activity, depressed mood, cognitive functions and might even affect heart function [18-20]. As a result, one in ten over the age of 50, and one in five over the age of 60 may be found to have hypogonadal levels of serum T (< 300mg/dl) [14, 21]. Nowadays overt hypogonadal men can, however, be treated by means of different T preparations [22] or rather, when associated with those clinical conditions (obesity, metabolic syndrome, type 2 diabetes mellitus, etc) often underpinning or causing T reduction in adult and elderly men, lifestyle changes and drugs targeting obesity and diabetes mellitus should be even taken into consideration [23].

In male, hypogonadism is considered an important factor in the derangement of cognitive function and physical performance [24, 25], given that T is considered as having a neuroprotective role [26-28]. Cognitive impairment, in fact, could be an important element of the clinical picture in subjects suffering from androgen-insensitivity syndrome [29] as well as both in young subject affected by primary (Klinefelter Syndrome) and secondary hypogonadism [30, 31] and in patients affected by late-onset hypogonadism (LOH). Moreover, in adult-elderly men a decrease of serum T levels [32, 33] and an increase of serum SHBG levels [34, 35] are associated with a higher risk of AD. This being the case, hormone therapy, particularly Testosterone replacement therapy (TRT) has been suggested to prevent or improve cognitive dysfunction or to prevent the onset of dementia in men with TDS.

This review aims to analyze and sum up the current clinical evidence about the possible relationship between serum T reduction and cognitive function in older men.

METHODS

An accurate research was made in PubMed and Embase databases using the following criteria: observational studies, clinical trials, randomized controlled trials, review papers and meta-analysis published in English in peer-reviewed journals after 1990. Keywords used were: male hypogonadism, late-onset hypogonadism, testosterone therapy, cognitive dysfunctions, and ageing male. All those papers which did not meet the above-mentioned initial search criteria were excluded. Finally, patents pertinent to T and its related compounds were examined. As a matter of fact, we conducted a detailed search on line of the most relevant recent (2010-2015) patents (in particular in www.google.com/paptens, www.uspto.gov, http://espacenet.com, www.freepaptensonline.com, www.wipo.int/pctdb/en/search-simp.jsp, www.freshpaptents.com and www.scopus.com) in order to identify more suitable ones for T substitution in patients suffering both from cognitive disorders and T deficit.

MAJOR EFFECTS OF T IN THE ADULT BRAIN

So far, the organizational effect as well as the neurotrophic and neuroprotective mechanisms of T on the adult brain has not been wholly understood yet. Current evidence has been obtained either from *in vitro* research or from preclinical observational studies.

As in other target tissues, T can be metabolized in dihydrotestosterone (DHT) (by means of the 5α reductase enzyme) or converted into 17βestradiol (by means of the aromatase enzyme) in the brain. As a result, T and DHT bind androgen receptor (AR), while 17βestradiol (E2) binds estrogen receptor (ER). Ultimately, AR intracellular signalling can modify gene expressions such as CREB activation [36]. Both aromatase and 5α reductase enzymes as well as AR and ER are found in the key regions of the brain involved in spatial learning and memory such as in the hippocampus and in the amygdale [37, 38]. Furthermore, a smaller hippocampus volume has been found in those subjects with lower free T and at least a copy of Apolipoproteine E polymophismε4 which is considered as a risk factor for AD (Table **1**) [39].

Table 1. Major Proposed Effects of T and its Active Metabolite in the Brain.

Nurotrophic role of T
1. Nuclear effects modifying gene expression (i.e. CREB activation)
2. Cell differentiation and neurite growth
3. Development of motor and autonomic neurons
4. Regulation of glial activity
Nuroprotective role of T
1. Stress antioxidant effects
2. Anti-apoptotic effects of neuronal cells
3. Up-regulating nerve growth factor (NGF)
4. Stimulating basal respiration and mitochondrial membrane potential

In addition, ARs are exclusively found in asymmetric synapses [40], while ERs are localized in both asymmetric and symmetric synapses [41].

Testosterone has been found to have neuroprotective effects against oxidative stress [42] and cell apoptosis [43]. Furthermore, the neuroprotective effect of T may be mediated by the positive effect of T in increasing the concentration of the nerve growth factor (NGF) in the hippocampus and in up-regulating its receptor in the forebrain [44].

Different *in vitro* studies (Table **1**) carried out either in animals or in humans, have demonstrated an active neuroprotective role of T in the processes involved in AD. As a matter of fact, in male double-transgenic mice the increase of T corresponds to a decrease in β-secretase, an enzyme responsible for the cleavage of the amyloid β protein precursor [13, 45]. In culture of hyppocampal neurons, T may reduce β-amyloid induced neurotoxicity [46], while preserving the integrity of neurites, reducing the expression of oligomeric β-amyloid peptide on presynaptic terminals. Moreover, these effects seem to be independent of estrogens and their receptor, as that positive effect did not change when letrozole (an aromatase inhibitor) was added [47]. Finally, T was more effective in alleviating β-amyloid induced mitochondrial bioenergetic deficits in cultures of human neuroblastoma cells [48]. Recently, in a human SH-SY5Y neuroblastoma culture study, T increased ATP level, basal respiration and mitochondrial membrane potential [49]. It has been proposed, therefore, that T may regulate energy production by inducing nuclear and mitochondrial oxidative phosphorylation (OXPHOS) genes, given that subunit mitochondrial chain complexes are encoded by nuclear and the mitochondrial genome, respectively, and both contain hormone responsive elements [50].

In hypogonadal men, preclinical studies conducted by using imaging techniques have shown some interesting data about the different brain region activations before or after a short time (3-4 weeks) of replacement therapy. For instance, Zitzmann *et al.* [51], studying the cerebral glucose metabolism by 18F deoxyglucose positron emission tomography during standardized mental rotation task in 6 hypogonadal men before and after TRT, showed that T substitution improved visuospatial performance with cerebral glucose metabolism enhancement during the test. In hypogndal men, using single photon emission computed tomography, TRT was able to increase the cerebral perfusion in the midbrain and the superior frontal gyrus, while the midcingulate gyrus turned out to be active after 3 months of TRT [52]. Furthermore, in female-to male transexualism T therapy has an enhancing effect on spatial ability performance, while an opposite effect is described in male-to female transexualism receiving an androgen deprivation therapy [53].

Finally, androgen deprivation therapy (ADT) (whether it is chemical or surgical) which is routinely used in the treatment of prostate cancer, may be regarded as an interesting model to study the effect of T withdrawal on cognitive function in men. In an observational study of over 40 men with prostate cancer who were treated with chemical ADT for 36 months, the impairment of cognitive functions was correlated with the rise in serum β-amyloid levels, while the discontinuation of that treatment improved their cognitive functions [54]. Another study carried out in 26 older men suffering from prostate cancer provided a selective decline in cognitive performance over 6 and 12 months with ADT, with visuomotor skills slowing down, reduced reaction time and working memory [55]. Nineteen men with prostate cancer who underwent chemical ADT, showed a worsened spatial rotation score, but an improved score for verbal memory during that therapy [56]. Lastly, two recent studies have found that men receiving ADT because of prostate cancer, experienced more symptoms of fatigue than those related to an impairment of cognitive performance [57, 58]. In conclusion, this preliminary evidence suggests that treatments reducing serum T levels in men with prostate cancer may impair performance in some cognitive domains especially in spatial ability. Further studies are needed, however, to determine the suitability of ADT as a model for determining hormonal effects on cognitive functions given the time spans of those studies and, in particular, the frequent presence of important comorbidities (i.e. metabolic diseases, hypertension and osteoporosis, etc.) in these patients [59, 60].

COGNITIVE FUNCTIONS AND TDS STUDIES

Although several studies have been conducted about the relationship between TDS and cognitive functions in men suffering from hypogonadism, many questions remain unsolved. Indeed, the appropriate study population has not been established yet, while the interventional studies have not shown wholly consistent results, being the randomized controlled trials (RCT) still limited.

In the next pages, however, we have summarized the principal observational and interventional studies about T and cognitive-related outcomes in hypogonadal men [60].

Observational Studies

Almost all of the cross-sectional studies carried out in different western countries consisting of a large number of participants with middle-old age (50-80 years), have supported the relationship between low circulating (F)T levels and poor cognitive performance [32, 35, 61-64]. Moreover, some of them [35, 61] also showed that E2 levels were inversely correlated with cognitive functions in hypogonadal men. Only two surveys [65, 66] found no association between T (and its free fraction) and various cognitive measurements. Although those researches have been well conducted and the data adjusted for age, education and in some studies co-variants such as alcohol consumption, body mass index (BMI) and depression were taken into account in the statistical analysis, all of the studies had a potential limitation which consisted in the fact that the method employed to measure serum T and E2 was the immunoassays instead of the mass spectrometry and no studies were carried out measuring serum FT [32] by dialitic method which is commonly considered the gold standard [67].

Given that cross-sectional studies cannot examine the outcome of dementia and although some longitudinal studies were carried out on a large number of men with the average age of 50-80, they were not able to infer the direction of causality, as all cross-sectional studies do. In particular, in 2 studies the examined population observed for 10 and 19 years, respectively, showed the association of high T/SHBG ratio with low risk to develop Alzheimer's dementia [1, 68]. Conversely, other 2 longitudinal analysis of a large number of men aged 71-93, one from the Honolulu-Asian Aging Study followed for a mean of over 6 years and the second one from the Osteoporosis Fractures Study [69], did not present that association, rather showing that higher bio-available E2 levels predict increased incidence of AD [70].Therefore, these latest studies added further complexity to the relationship between sex hormone levels and cognitive function impairment in men. However, even though the published data

have limitations, on balance those studies suggested the association between low serum T levels and, to a limited extent, low E2 levels with impairment of cognitive function in middle-aged and old men [60].

Intervention Studies of Testosterone Treatment on Cognitive Functions

Several randomized placebo-controlled trials (RCTs) aiming to verify the positive effects on cognitive function in men have been carried out so far (Table **2**). However, the results may be regarded as being inconclusive because of the following reasons: limited number of participants, different T formulation used, duration of treatment, range of cognitive tests and outcomes [71].

Most of the RCTs lasted up to 12 weeks, yielded a significant enhancement of spatial cognition in middle-aged and old males, while other cognitive functions such as verbal memory, dexterity and cognitive flexibility were not positively affected [72, 73]. Conversely, in three studies of which 2 were of the duration of 1 year, no effect of T therapy on cognitive functions was observed [74-76]. However, besides those inconclusive and still open results obtained in middle-aged and old men, it is remarkable the fact that T replacement therapy improved the cognitive impairment caused by suppression of endogenous T productions by means of Levonorgestrel (LN) [77] or GnRH agonist [78] in young men (21-45 years old).

Interestingly, two principal metabolites of T (E2 and DHT) may have some effects on specific areas of cognitive performance. Indeed, E2 and DHT might improve cognitive functions in terms of verbal memory or attention, respectively. Cherrier *et al.* [79] showed that in a 6 weeks study in which subjects were given intramuscularly T (100mg/week) with and without an aromatase inhibitor (anastazole orally 1mg/day), only those men receiving T alone enhanced verbal memory. Another study by Cherrier *et al.* [80] compared a group of old men with hypogonadism on T gel therapy with another group on DHT gel. In this research, there wasn't a placebo group. T treated men showed an improvement of verbal memory, whilst those treated with DHT enhanced spatial memory. Finally, Vaughan *et al.* [81] conducted a study in which 60-86 year-old men showed low-normal levels of T (< 350mg/dl) and were treated with T (100mg intramuscularly/2 weeks) with or without oral Finasteride (5mg/day) which inhibits the conversion of T into DHT. Although several cognitive functions did not show treatment-related differences, attention was enhanced in those subjects treated only with T, while verbal functions improved in those who were given T and Finasteride. However, it is worth underlining that additional studies are needed to verify and clarify the possible benefits of rising serum E2 and/or DHT levels in order to improve different cognitive activities in men [60].

Some studies, however, highlighted the role the serum T levels might have reached during the therapy in comparison with the obtained effects on the cognitive function in men. Different researches [82, 83], in fact, some of the RCTs [78, 84], have borne out the importance of T levels achieved during TRT in the study in relation to cognitive functions. As a matter of fact, if the effects of TRT on body composition and, in particular, the enhancement of muscle mass could be obtained by means of normal T levels, the effects on different cognitive outcomes can be obtained reaching higher serum T levels, for instance giving an injection of 100 or 300 mg of T [78, 80, 83-85]. This evidence, in fact, bears out those data that, in the elderly men, psychosomatic complaints and metabolic risk are related to testosterone levels in a symptom-specific manner [86]. The work of Gray *et al.* can be considered on same wavelength [87]. They examined the effects of graded testosterone doses on sexual function, mood, and visuospatial cognition in healthy, older men (age, 60-75yr) who were given a long-acting GnRH agonist to suppress endogenous testosterone production and were randomized to receive one of five doses (25, 50, 125, 300, and 600 mg) of testosterone enanthate weekly for 20wk. Although, no effects of testosterone dose were observed on two measures of mood (Hamilton's Depression Inventory and Young's Mania Scale), the authors found differences in visuospatial cognition across treatment groups, with highest scores in men on highest dose (600mg/week). Conversely, Maki *et al.* [88] gave testosterone enanthate (200mg i.m. every other week for 90d) crossed over with placebo to 50 cognitively normal eugonadal men, aged 66-86yr. Performance was assessed on a standardized verbal memory test, and brain activity (relative glucose metabolic rates) in medial temporal and frontal regions was measured with positron emission tomography during a verbal memory task. Although that treatment was able to increase serum T by 241%, the behavioral results showed a significant decrease in short-delay verbal memory with treatment and a non-significant decrease on a composite verbal memory measure. On the other hand, Positron emission tomography scans revealed a relative decreased activity in ventromedial temporal cortex (i.e. right amygdala/entorhinal cortex) and a relative increased activity in bilateral prefrontal cortex with treatment. In conclusion, decreased verbal memory and altered relative activity in medial temporal and prefrontal regions suggest possible detrimental effects of supraphysiological testosterone supplementation in elderly men.

Intervention Studies of Testosterone Treatment on Dementia

So far, relatively few randomized placebo controlled studies aiming at improving the cognitive functions have been carried out about TRT in men suffering from dementia (Table **2**). Those studies made up of populations of some old men (> 70 years old) affected by AD [27, 89, 90], while others with MCI [27, 91], lasting between 6 to 52 weeks, showed, beside the improvement of quality of life, a significant enhancement of visual-spatial ability, spatial memory and verbal memory. However, the possible role of aromatization of T into E2 on cognitive outcomes in patients with AD and MCI needs further experiences [91].

REVIEWING RECENT PATENTS

An extensive evaluation of the most recent patents (ranging from 2010 to 2015) was carried out in order to verify the most appropriate ones for the treatment of patients with T deficit and cognitive disorders. Taking into consideration the

Table 2. Testosterone Treatment and Cognitive Functions: Intervention Studies.

Study/Author/Year	Age (Yrs) (m/ Range)	Duration (Weeks)	Dose	Results	Ref.
Cherrier 2005 (CI or AD)	63-85	6	T 100mg im weekly	Improved spatial memory and ability, and verbal memory; No differences in verbal fluency or attention	[27]
Janowsky 1994	67.4	12	T (scrotal patch) 15mg/daily	Improved spatial cognition. No effect on verbal memory, dexterity and cognitive flexibility	[72]
Cherrier 2001	50-80	6	T (im) 100mg/weekly	Improved spatial memory and ability, and verbal memory; No effect on attention or verbal fluency	[73]
Sih 1997	51-79	52	T (im) 200mg/2 weekly	No effect on memory, recall or verbal fluency	[74]
Kenny 2002	76.4	52	T 2.5mg patch daily	No difference in cognitive test results between groups	[75]
Kenny 2004	80	12	T 200mg im 3 weekly	No difference in cognitive test results between groups	[76]
Cherrier 2002	21-46	8	T (im) 100mg/weekly + LN 125mcg oral/day	Decreased performance in tests of verbal memory in LN-treated group, improved selective attention in T + LN group	[77]
Young 2010	25-35 60-80	6	GnRH suppression, T gel 100 or 75mg im ±AN 1 mg/day oral	On-treatment free T or free E2 positively associated with spatial cognition; On-treatment free E2 negatively associated with working memory	[78]
Cherrier 2005	50-90	6	T 100mg im weekly ± AN 1 mg oral/day	Improved spatial memory in T and T + AN groups, improved verbal memory in T group only	[79]
Vaughan 2007	65-83	156	T 200mg im 2 weekly± F 5mg oral/day	No differences in multiple cognitive tests; except for improved verbal memory with T + F, improved attention with T only	[81]
Haren 2005	60-86	52	T 80mg oral (twice daily)	No difference in visuomotor tracking and visuospatial ability	[82]
Emmelot-Yonk 2008	60-80	26	T 80mg oral (twice daily)	No differences in verbal memory, perceptual speed, attention, or visuospatial performance	[83]
Cherrier 2007	50-90	6	T 50, 100 or 200mg im weekly	Improved verbal and spatial memory associated with moderate increases in T, not with low or large increases	[84]
Gray 2005	60-75	20	GnRH suppression + T 25, 50, 125, 300, 600mg im weekly	Differences in visuospatial cognition across treatment groups, with highest scores in men on highest dose (600mg/week)	[87]
Maki 2007	66-86	13	T 200mg im 2 weekly	No difference in working memory and attention, decreased recall	[88]
Tan 2003 (CI or AD)	68-80	52	T 200mg im 2 weekly	Improved general cognition and visuospatial ability	[89]
Lu 2006 (CI or AD)	69.8 62.3	24	T gel 75mg daily	Trend to improvement in visuospatial function in AD men, no difference in verbal memory	[90]
Sherwin 2011 (CI or AD)	75.9	12	E2 1mg oral daily	Improvement in verbal memory; No differences in global cognitive function or visuospatial ability	[91]

Legends: T: Testosterone, LN: Levonorgestrel, AN: Astanazole, F: Finasteride, E2: Estradiol, AD: Alzheimers' Disease, CI: Cognitive Impairment

goals for accurate TRT in adult men with T deficiency and suffering from cognitive dysfunction as well as the therapeutic appropriateness and the potential adverse effects of TRT in adult and/or elderly men [22], we considered some of them as being unsuitable. In particular, the association of T with selective serotonin reuptake inhibitors such as buspirone drug [92] which is given for male sexual dysfunction, while pharmaceutical agent that can enhance serum T or encapsulated cells (ovary cells) for T treatment should be regarded as inappropriate treatment either for the difficulty to obtain adequate range of T levels or for the technical difficulties [93, 94]. In addition, the compound consisting in T plus anastrozole should be not considered as an appropriate T substitution, given that the aromatase inhibitor role of anastrozole might cause a reduction of bone mass density in hypogonadal patients who generally could suffer from osteoporosis [95] while the ones administerd nasally (spray and gel) were less easy to use, often causing nasal discomfort, nasopharyngitis, bronchitis, upper respiratory tract infection, sinusitis, and nasal scab [96, 97].

Those patents which propone T therapy given transcutaneously or perorally can be adequate formulations for TRT [98-106], although it is worthy reporting that oral T compounds (T undecanoate) can raise serum DHT levels which is not advisable in elderly men [107], while percutaneous ones have a large within-individual variations in serum T, showing, therefore, a higher variability of its plasma levels [108]. It is interesting the patent which, using transdermal preparations (sprays, lotions, pastes, creams, etc) of clomiphene-like selective estrogen receptor modulator (SERM), can increase serum T levels in hypogonadal men [109]. As a matter of fact, this compound given orally can increase serum T levels both in obese hypogonadal men and in those with infertility, avoiding the possible side effects that TRT might determine in adult and elderly men [110, 111]. Finally, a recent patent characterized by a compound that stimulates the production of T through transmucosal administration is proposed as a treatment aiming at preventing the onset of Alzheimer's diseases. This product is a truffle extract that provides an olfactory stimulus by smelling T that is, naturally, contained in any type of truffle [112]. However, to date, there has been no clinical evidence about patents compound in hypogonadal old men affected by cognitive dysfunction.

CURRENT & FUTURE DEVELOPMENTS

Although a considerable amount of *in vitro* and *in vivo* evidence points out the relationship between T declining (as does aging male) and cognitive dysfunctions, they are not considered as specific signs or symptoms for the overt hypogonadism in young and adult men [113]. Indeed, TRT has not been envisaged for the cognitive disorders in the International guidelines for the diagnosis and treatment of male hypogonadism [113], while T substitution has been suggested for hypogonadal men suffering from depression [114]. Indeed, these inconclusive results could stem from the fact that the data that have been provided so far, were collected in population made up of small number of participants, often observed for a short period of time and by a determination of T by means of those methods which should not be considered as being accurate. In addition, there have been limited RCT results of TRT in elderly men with MCI and or dementia where the risks versus the benefit of hormonal substitution have been carefully considered [114]. However, it is worth of note underlining that young and adult patients with overt hypogonadism often complain of cognitive dysfunctions which can be overcome by means of TRT [60]. In conclusion, it is desirable that further randomized controlled studies should be conducted even by means of accurate methods for the measurement of serum T and its free fraction.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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