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Testosterone, mood, behaviour and quality of life

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Abstract

Testosterone plays a pivotal role in maintaining balance within the multi-dimensional psychological network of mood, behaviour, self-perception and perceived quality of life in men of any age. Apart from classical forms of hypogonadism, low testosterone concentrations can also be seen in older men, described as an age- and comorbidity-driven functional hypogonadism and might relate to depressive symptoms exhibiting a wide array of clinical pictures ranging from dysthymia and fatigue over inertia, listlessness to hopelessness and suicidal thoughts. Also, various traits of anxiety, from unfocussed fear to phobic anxiousness and open panic syndromes, are influenced by testosterone. Correspondingly, anxiolysis is likely to be modulated by testosterone via stress resilience, threat vigilance and reward processing. The steroid modulates pro-active and re-active dimensions of aggression, which has to be seen within the context of gaining or maintaining status. This may also include other strategies impacting the social position: heroic or parochial altruism and non-aggressive paths of assertiveness, such as posture and social vigilance. Independent rather than relationship-associated self-construal and self-esteem influence risk-taking traits under the modulation of testosterone. In addition, the genetic setting of the androgen receptor modulates the role of testosterone in aspects regarding mood and personality. Dimensions of sexuality are rather important in this context, but are not target of this article and covered in another part of this special edition. Overall, the quality of life in older hypogonadal men can be positively influenced by testosterone substitution, as has been demonstrated in large placebo-controlled trials.

KEYWORDS

androgen receptor, behaviour, depression, mood, testosterone

1 | INTRODUCTION

Testosterone is believed to support maintenance of psychological features representing positive and negative affects within a balance, which is perceived as 'good mood' and an enjoyable quality of life. Correspondingly, a deterioration of general 'good mood' and factors involved in the overall quality of life has been described as a complex of symptoms related to male hypogonadism.[1-3] In older men with age- and comorbidity-related decreased serum testosterone concentrations, a condition named functional or late-onset hypogonadism, symptoms such as dysphoria, low vigour and vitality, irritability, lack of assertiveness and depression are more likely to be present than in eugonadal men.[4-6] In the European Ageing Male Study describing a cohort of elderly men, low testosterone levels

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were found to be associated with features of fatigue and depression.[7] In agreement, men undergoing androgen-deprivation therapy for prostate cancer exhibited mood disturbances such as anxiety, fatigue and lack of vitality.[8]

In the past, unprovoked aggressive behaviour and violence were found to be related to serum testosterone concentrations levels in humans and animals. Men with physically and verbally aggressive behaviour or social dominance had significantly higher levels of serum testosterone compared with non-aggressive subjects.[9-11] Recently, this is seen in a more complex manner. For example, serum testosterone levels are rather associated with risk-taking behaviour and traits of reactive aggression.[12-14] This effect of testosterone may be more pronounced in men exhibiting an independent self-construal, which is an individualistic view or concept of self.[15] Overall, testosterone is now understood to drive a general repertoire of motivated behaviours, often subsumed under the concept of dominance behaviour. Such concepts refer to the motivation of an individual to achieve or maintain a high social status, which can also be achieved non-aggressively.[16]

Thus, testosterone might influence an underlying motive rather than aggression per se. For instance, rhesus monkeys with high testosterone levels use stares, threats and displacements, rather than overtly aggressive interactions, to ascertain high social status.[17] In humans, status is asserted on similar paths, being related to testosterone concentrations: face-to-face interactions by increased duration of staring and speech as well as body postures displaying supremacy. In addition, acts of so-called heroic or parochial altruism, which is an increased proposer generosity in interactions within a group to achieve a personal advantage, seem to be related to testosterone.[18-21]

Hence, testosterone is a multi-faceted effector of psychological traits, ranging from general mood to modification of interaction with others.

2 | OVERALL QUALITY OF LIFE AND MOOD

Quality of life (QoL) is a summary of psychological variables, which contribute to the subjective perception that life is worthwhile. QoL is principally the degree to which a person enjoys the possibilities of life, based on the categories 'being', 'belonging' and 'becoming', respectively, who one is, how one is connected to one's environment and whether one achieves one's personal goals, hopes and aspirations. Thus, QoL is a multi-dimensional construct comprising the individual's physical, mental and social well-being, each including both cognitive and emotional components.[22] Items contributing to the impression of QoL are the ability to perceive enjoyment of life in balance with perceived stress, a general motivation in life as well as overall work performance, self-confidence and the ability to focus, the subjective energy in life and the abilities to cope.[22] This also includes, in most men, parameters of sexual nature. These latter are considered within another article of this issue but are, nevertheless, always a part of the questionnaires recruited to estimate QoL.

A meta-analysis on testosterone replacement treatment (TRT) in hypogonadal men vs placebo evaluated 23 randomized controlled trials (21 were placebo-controlled, two were active-controlled) involving 3090 participants. Compared with placebo, treatment with any TRT significantly improved quality of life (standardized mean difference −0.26, 95% CI −0.41 to −0.11, $P < .001$). The effect was largely attenuated in men with symptoms of depression.[23]

Another meta-analysis evaluated sixteen trials with a total of 944 subjects. An overall positive impact of TRT on general mood was seen with an effect size of 4.592 ($P < .0001$), which was age-dependent: a subgroup of men aged less than 60 years exhibited an effect size of 5.279 ($P < .0001$) while the effect size was not statistically significant in men older than 60 years. The effect size in hypogonadal men was 4.192 ($P < .0001$), whereas the result was not statistically significant in eugonadal men. In agreement with the aforementioned analysis, the effect size was larger in with subthreshold depression compared to those with major depression.[24]

Corresponding results regarding the factor 'general energy' were seen in a randomized, multicentre, double-blinded, placebo-controlled, 16-week study of 715 hypogonadal symptomatic men (median age 55.3 years, range 19–92 years) receiving placebo or a topical testosterone solution for TRT. Patient-reported improvements in general energy using the Patient Global Impression Questionnaire showed a significant effect of TRT ($P < .001$). Age less than 45 years and lower baseline testosterone levels had a significant influence on a more pronounced outcome of TRT. In addition, men with forms of classical hypogonadism had a larger benefit from TRT than men with functional hypogonadism.[25] As comorbidities are found especially in functional hypogonadism and, hence, mostly in elderly men, these underlying pathologies might have, apart from hypogonadism as such, an intrinsic additional impact on QoL and psychological functions. In afflicted men, the treatment of hypogonadism is likely to attenuate symptoms, albeit not fully. Thus, it is paramount and a prerequisite that comorbidities are treated adequately to improve QoL and well-being. This is in agreement with the EAA guidelines on functional hypogonadism.[1]

To assess effects of TRT in older men with functional hypogonadism, a well-characterized cohort of 788 community-dwelling, relatively healthy, older men of at least 65 years of age with well-defined symptoms and with a restricted range of low testosterone levels (excluding both severely low and borderline low T levels) was recruited. Within a double-blind, placebo-controlled trial using transdermal testosterone gel, the total group using *verum* exhibited marked changes compared with placebo. Physical function as assessed by the 6-min walking test and the physical function test increased significantly vs placebo ($P = .007$ and $P = .002$, respectively). Similarly, changes in the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue score, the SF-36 vitality score, the PANAS positive and negative affect scores and the overall subjective 'energy level' were significantly improved in the total group of men receiving TRT compared with placebo. Notwithstanding, the

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effects were largely attenuated in a smaller subgroup selected for this analysis.[26,27]

Another double-blind placebo-controlled trial focussed on older men with type 2 diabetes mellitus and simultaneously presents functional hypogonadism. 199 men received intramuscular testosterone undecanoate vs placebo for 30 weeks. Measures to determine QoL were scores assessed by the Aging Male Symptom (AMS) Scale, validation of depression and anxiety based on the Hospital Anxiety and Depression Scale (HADS) and overall quality of life based on a global efficacy question (GEQ). GEQ scores improved significantly in men receiving testosterone vs those receiving placebo ($P < .001$), while there were no significant results for the AMS and HADS domains. However, when the latter scores were stratified for clinical depression, there was a marked improvement in men receiving TRT who were not depressed (HADS: $P = .03$ and AMS: $P = .02$). This is in agreement with the meta-analysis mentioned above. Depression seems to be a major confounder on effects of TRT in hypogonadal men, when QoL is assessed.[28]

Similar to this trial, positive effects of TRT on QoL were seen in larger cohorts of hypogonadal men of up to more than 1.000 patients in uncontrolled 'real-life' settings or registries.[29,30] A smaller uncontrolled study comparing two different intramuscular testosterone preparations for TRT in 40 hypogonadal men described marked improvements in scales of sociability, concentration, agitation, self-confidence, listlessness, dizziness, activation, depression, fatigue, anxiety, good mood and aggression.[31]

It is evident that hypogonadism can have a negative impact on quality of life and mood. Testosterone substitution is seen as a means to improve these parameters.[2] However, if these psychological symptoms are the only problems of the patient, the use of TRT to improve quality of life and mood in men with hypogonadism is currently not strongly recommended.[1]

3 | DEPRESSION

Depressive symptoms, ranging from dysthymia to major depressive disorders, represent psychiatric conditions with severe personal consequences. More than 100 million men are currently affected by various forms of depression.[32] Testosterone is a neuroactive steroid influencing mood and appetitive behaviour,[33] which has been demonstrated by animal models of depression in which testosterone administration increased serotonin release in the dorsal raphe nuclei as well as it induced neuroplasticity in the hippocampal formation.[34-36] Both, increased serotonin release and novel neuronal connections, are central mechanisms of antidepression, as they can promote positive patterns of thought and self-experience.[37]

The European Male Aging Study demonstrated that depression in its various forms is related to hypogonadism in community-dwelling older men, with a potentially mutual causal relationship.[38] Such a relation was also shown in a clinical sample of 296 older men, in whom symptoms of dysthymia, fatigue, inertia and listlessness and major depression were related both to serum testosterone concentrations and to the genetic modulation of androgen effects by the CAG repeat polymorphism within the androgen receptor gene.[5,6] This is substantiated by a longitudinal investigation in 748 older men, in whom the 2-year incidence of a newly diagnosed depressive illness was 18.5% in men with previous hypogonadism vs. 10.4% in controls ($P = .006$). After adjustment for age and medical morbidities, men with hypogonadism had a shorter time to develop a depressive illness (adjusted hazard ratio = 2.1; 95% CI = 1.3–3.2, $P = .002$).[4]

A randomized, double-blind, placebo-controlled study in 33 hypogonadal men with a concomitant subthreshold depression (dysthymia or minor depression) investigated the effects of either testosterone gel or placebo gel. Men on TRT had a greater reduction in scores of the Hamilton Rating Scale for Depression ($P = .024$) and a higher remission rate of subthreshold depression (52.9% vs. 18.8%, $P = .041$).[39] Correspondingly, a larger double-blind placebo-controlled trial in 788 older men with functional hypogonadism (see above) improved depressive symptoms demonstrated as lowering scores on the Patient Health Questionnaire 9: the treatment effect was −0.72 (95% CI: −1.20 to −0.23) ($P = .004$).[26,27] Also, a randomized, placebo-controlled, double-blind trial in 184 hypogonadal men receiving intramuscular testosterone undecanoate vs placebo demonstrated a marked decrease in the Beck Depression Inventory in the men receiving TRT (mean difference vs. placebo after 30 weeks: −2.5 points; 95% confidence interval [CI]: −0.9; −4.1; $P = .003$).[40]

A meta-analysis involving 11 placebo-controlled and 1 active-controlled trial with altogether 852 participants evaluated depression indices. Compared with placebo, any TRT improved depression (SMD −0.23, 95% CI −0.44 to −0.01; $P < .001$).[23] Another meta-analysis included only double-blind placebo-controlled trials, which used the Hamilton Rating Scale for Depression. Seven studies involving 364 men showed a significant positive effect of TRT in depressed patients when compared to placebo ($z = 4.04$, $P < .001$).[41] A recent random-effects meta-analysis of 27 randomized controlled trials including 1890 men demonstrated that TRT is associated with a significant reduction in depressive symptoms compared with placebo (Hedges' $g = 0.21$ [effect size according to Bessel's correction of Cohen's d]; 95% CI: 0.10–0.32, $P < .001$), showing an odds ratio of efficacy = 2.30 (95% CI: 1.30–4.06, $P = .004$). These effects exceed the efficacy thresholds for pharmacologic agents for depression therapy proposed by the National Institute for Health and Care Excellence guidelines for treatment-resistant depression.[42-44]

The association between testosterone and erectile function is well-known, and likewise, the association between mood disorders (including depression and anxiety) and sexual dysfunction is supported by solid evidence. However, it is also true that sexual dysfunction might cause depression because of the negative psychological burden associated with it. Hence, testosterone treatment in hypogonadal patients might actually be beneficial to psychological symptoms both directly and indirectly by improving erectile function (see article about sexual function in this special edition).

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Thus, symptoms of depression can be mitigated in hypogonadal men using TRT. Still preferential is the use of established anti-depressive therapies, cognitive behavioural approaches and psychiatric consultation in patients with first-line depressive symptoms or in those with diagnosed major depression.[1] Nevertheless, additional testosterone supplementation can improve the outcome of such therapies if the patient is hypogonadal.[42]

4 | ANXIETY

The putative associations of testosterone with anxiety and its escalating variants phobic anxiety and panic disorder have not been investigated extensively. In male rodents, induction of higher testosterone levels led to reduction in anxiety.[45,46] In humans, lower testosterone concentrations and a general tendency to develop unfocussed anxiety have been described.[8,47,48] An inverse correlation between symptoms of anxiety assessed with the Hopkins Symptom Checklist with total and free testosterone in a population-based sample of 3413 men was reported.[49] A correlation between testosterone and free-floating anxiety and phobic anxiety in a sample of 2042 male patients with sexual dysfunction was reported, as well.[50] A clinical sample of 296 older men exhibited a marked association of anxiety traits (higher anxiety, panic and phobic anxiety levels) assessed with the Brief Symptom Inventory and the Patient Health Questionnaire-9 with the genetically modulated androgen activity via the CAG repeat polymorphism of the androgen receptor gene but not directly with serum testosterone levels.[51]

Anxiolysis, on the other hand, might be induced by testosterone.[45] The mechanisms by which testosterone might exert such effects are four suggested channels of anxiolysis: threat vigilance, reward processing, general fear reduction (leading to lower fear-related attentional bias) and stress resilience.[18]

5 | AGGRESSION

Testosterone is often described as a pivotal moderator of aggression. There is evidence by castration and replacement experiments in animals that testosterone can drive aggression. Regarding humans, the testosterone/aggression complex is most likely not static but rather fluctuates in response to cues of challenge originating from the environment.[52] Such challenge-induced fluctuations may strongly regulate situation-specific aggressive behaviour. In meta-analyses, baseline testosterone levels are weakly associated with aggression (r = 0.071, 95% CI: 0.041–0.101). Also, increments of testosterone concentrations are positively associated with aggression (r = 0.162, 95% CI: 0.076–0.246)[52] (see below regarding anabolic steroids).

In a placebo-controlled, double-blind cross-over study using intramuscular (im) injections of testosterone undecanoate (TU), 28 eugonadal men were randomized into one of two treatment groups: A1) active, receiving 1000 mg TU im, followed by A2) washout, followed by A3) placebo, receiving 4 ml of oily vehicle im; B1) placebo, 4 ml of oily vehicle im; B2) washout followed by B3) active, receiving 1000 mg TU im Two-factor repeated-measures ANOVA found no significant effects on tension-anxiety, depression-dejection, vigour-activity or confusion-bewilderment. Interaction of effects could be described for a testosterone-related increase in anger-hostility and verbal, but not physical aggression and a reduction in fatigue-inertia. In response to aggressive provocations, direct aggression increased testosterone-dependently while irritability and assertiveness were not affected. Measures of self-esteem increased as well.[53] The study has the limitation of treating eugonadal men with a single injection of testosterone, thus facilitating a change of testosterone levels that is rather subtle compared to baseline.

6 | SELF-CONSTRUAL AS BASIS OF COMPETITIVENESS, SOCIAL STATUS, RISK-TAKING AND SELF-ESTEEM

Closely related to the finding in aggressive behaviour, it appears that testosterone promotes status-seeking and social dominance motives and thus plays an important role in social status hierarchies. A causality between social and emotional behaviour induced by testosterone might exist. Testosterone appears to have a complex role in driving behaviours that tend to increase an individual's motivation and ability to acquire as well as defend social status. Testosterone dynamics and psychopathic personality traits such as fearless dominance, coldheartedness and self-centred impulsivity independently predicting antagonistic behaviour towards persons perceived as 'inferior' have been reported.[54]

Such findings seem to be mediated by traits of self-construal. Self-construal refers to a person's view of self and structure of a self-schema. People with an independent self-construal hold a view of self that emphasizes the separateness of the individual, while an interdependent self-construal is associated with a self-view driven by relationships to others.[55] It is assumed that a dynamic reactivity of the hypothalamic-pituitary-gonadal axis to competition might promote aggression to take risks for personal gain in the independent self, while stable and resting levels of testosterone might attenuate aggression in the interdependent self. Thus, risk-taking behaviour in men with independent self-construals seems to be reinforced by testosterone, once they have seen a success in a competition for status. It is assumed that modulations of testosterone concentrations in independent people may affect status-seeking behaviours through personalized means (using force or obtaining economic resources) whereas changes in testosterone levels in more interdependent people would prompt more socially oriented status-seeking strategies (prosocial behaviour, generosity).[15,56] Pharmacologically induced higher testosterone levels augmented risk-taking behaviour under time-related circumstances in men with dispositional characteristics (dominance, impulsivity, independent self-construal): time pressure reduced cooperation and increased risk-taking, while in men with an interdependent self-construal, testosterone and time pressure led to seeking cooperation for help (total n = 400).[57]

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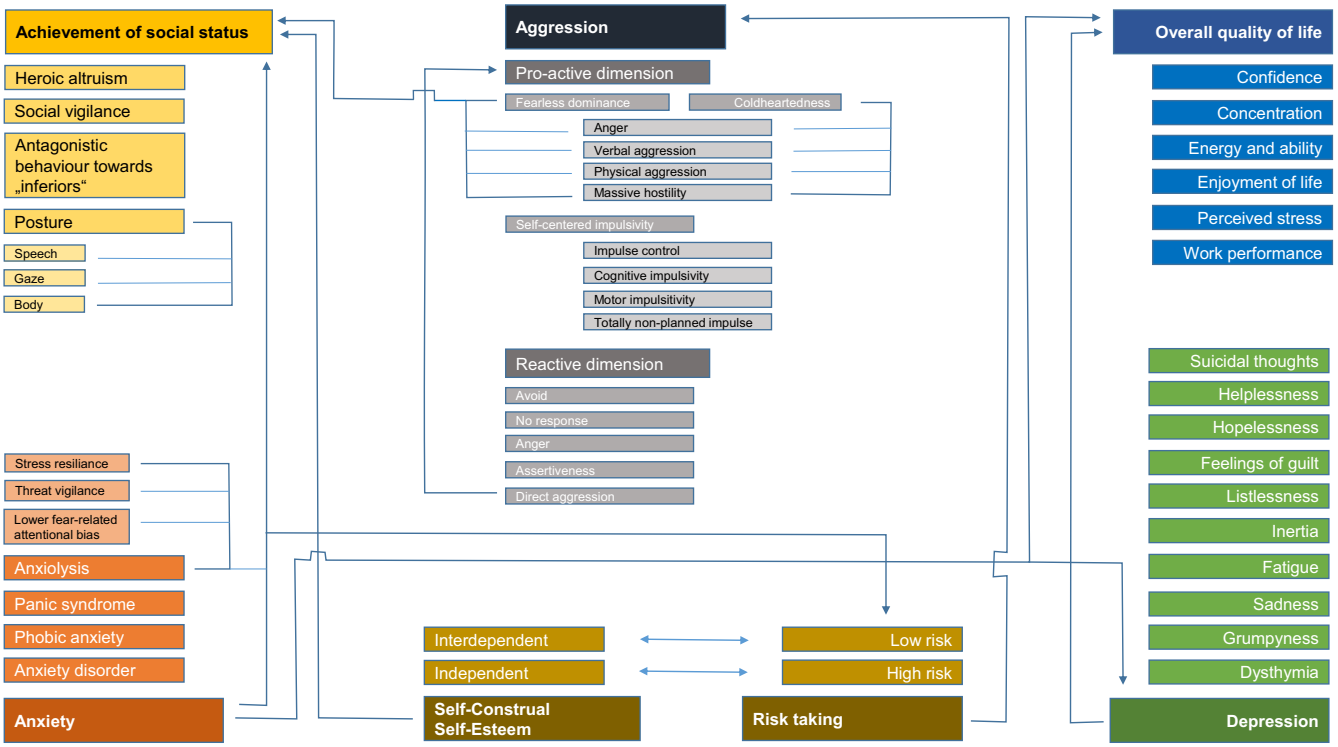

FIGURE 1 Characteristics of mood, behaviour and quality of life as being influenced by testosterone levels

Social status may also be gained by acts of so-called heroic or parochial altruism (being generous to gain an advantage, especially in regard to social status). Higher testosterone levels were shown to be associated with the preferential treatment of ingroup members, while aggression and discrimination was directed towards outgroup members.[20] Such behavioural characteristics seem to be reflected by morphological correlates as neural responses in the anterior insula and the ventromedial prefrontal cortex can be visualized in functional magnetic resonance images during respective tasks.[21]

Testosterone effects on behaviour are modulated by the androgen receptor gene CAG repeat polymorphism, as a psychopharmacogenetic approach in 308 men with independent self-construals revealed. Men with shorter repeats experienced a greater reward of testosterone-induced assertive behaviour.[58] This is corroborated by another study, in which higher testosterone levels and shorter CAG repeats were related to dominance as well as aggressive and non-aggressive risk-taking, while longer CAG repeats and lower testosterone were related to depression and lower self-esteem.[59] Similarly, short CAG repeats and higher testosterone levels were associated with measures of impulsivity in younger men: motor impulsiveness, cognitive impulsiveness and non-planning impulsiveness.[60] Higher testosterone levels and shorter androgen receptor gene CAG repeats are also associated with confidence and competitiveness in men.[61] Correspondingly, in a pharmacological trial in 173 men, exogenous testosterone vs. placebo increased motivation to compete for status, but only in individuals with an unstable low status or a stable high status and short CAG repeats. Men with a stable low status refrained from competition regardless of testosterone and genetic background.[62]

The question arises whether any evidence regarding differences between men with congenital and acquired hypogonadism in relation to behavioural characteristics exists. While it seems quite plausible that such differences could be present, there is no reliable research on this matter. One might assume, however, that men with congenital hypogonadism exhibit a different spectrum of behavioural traits than men with acquired forms of hypogonadism as they have never experienced and learned from the consequences of various types of androgen-related behaviour.[63,64]

7 | EFFECT OF ANABOLIC STEROIDS ON MOOD AND BEHAVIOUR

There is a widespread abuse of synthetic anabolic steroids which are metabolized differently compared with natural testosterone, for example these substances might not be aromatized or 5-alpha-reduced or might have intrinsic other binding capacities to receptors. An assumed side effect of anabolic androgenic steroids (AASs) is an induction of impulsive and uncontrolled behaviour, characterized by indiscriminate and (un-)provoked aggression (so-called 'roid rage'). Pubertal rats receiving AASs respond to social cues more aggressively towards intact males than do castrated controls. AASs might sensitize these animals to their surroundings and lower the threshold to respond to provocation with aggression. It was thus speculated that in humans, AAS exposure does not function as a proximal trigger for violence, but may increase the likelihood that aggressive reactions to provocation will result in violence, that is physical aggression eventually transforming into massive, harmful hostility („...when the monkey is high, you do not stare...'). As

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there are only case reports about 'roid rage', this subject remains debatable.[65-68] However, it has been demonstrated among adolescents, that psychiatric disorders, such as conduct disorders and sociopathies, can promote the switch to abuse AASs, thus being a trigger and not the result of AAS use.[69] Nevertheless, apart from the dimension of aggression, reports exist that AAS use can lead to profound effects on the brain and behaviour inducing poor impulse controls of anxiety and promote extreme mood swings from depression to mania or hypomania.[70-74] There are reports that sleeplessness, increased irritability, depression disorders as well as melancholy and anxiety may persist for many years in AAS users and former users.[75] Speculations exist that such processes have a morphological substrate in form of a lower connectivity between amygdala and frontal, striatal, limbic, hippocampal and visual cortical areas.[76]

8 | SUMMARY

In men, mood, behaviour and quality of life are influenced by testosterone. Marked effects on mood and behaviour can be facilitated by endogenous testosterone levels and external administration of the sex steroid. Such effects are likely to be mediated genetically by the CAG repeat androgen receptor polymorphism. Not all findings are robust, but it can be assumed that the multifaceted effects of testosterone, as summarized in Figure 1, can be influenced by low testosterone levels as found in hypogonadism and may be subject to restoration by testosterone replacement therapy. Well-being and quality of life in men are a function of testosterone.

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