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Association between nandrolone and behavioral alterations: A systematic review of preclinical studies

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ABSTRACT

Background and aim: In recent years the expanding misuse of Nandrolone among non-athletes, particularly adolescent males is a prevalent global concern due to its adverse effects. This article provides a summary of the experimental studies to clarify the relationship between Nandrolone exposure and behavioral and cognitive performances.

Materials and methods: The present systematic review was conducted using PubMed, Embase and ScienceDirect databases, from 2000 to 2020, using the following key terms: Nandrolone AND Cognition, Nandrolone AND Learning, Nandrolone AND Memory, Nandrolone AND (Synaptic plasticity or Hippocampal synaptic plasticity), Nandrolone AND (Aggression or Aggressive-like behavior), Nandrolone AND (Anxiety or Anxiety-like behavior), Nandrolone AND (Depression or Depressive-like behavior).

Results: 33 qualified papers were selected from the 2498 sources found. Of the 33 cases, 32 (96.97%) were males while only 1 (3.03%) was female and male. From 33 selected articles 8 reported studies were related to spatial memory, 2 reported studies were related to avoidance memory, 11 studies reported information on synaptic plasticity, 11 reported studies were related to aggressive behavior, 8 reported studies were related to aggressive behavior and 6 reported studies were related to depression.

Conclusion: Nandrolone can change spatial ability, avoidance memory and hippocampal synaptic plasticity. Also, Nandrolone exposure produces variable effects on behavioral function such as aggression, depression and anxiety. This despite the fact that the results are contradictory. These discrepancies might be due to the differences in sex, age, dosage and treatment duration, and administration route. However, the negative results are more common than the published positive ones.

1. Introduction

Anabolic androgenic steroids (AASs) are a large group of synthetic derivatives of the male gonadal hormone testosterone, which have both androgenic and anabolic effects [1-3]. Based on replacement of the base molecule, AASs are classified in 3 main classes. Esterification at C-17 is related to class I. Class II is related to a demethylated group at C-19 and may also have C-17 esters. Alkylation at C-17 creates class III. Nandrolone (19-nortestosterone) belongs to the second class of AASs [4,5]. The classification of AASs is presented in Fig. 1. Nandrolone usually used as esters, such as Nandrolone Decanoate (ND) and Nandrolone Phenylpropionate (NPP) (Fig. 2). The most commonly used esters are ND and to a lesser extent NPP [6]. Nandrolone esters were first described and introduced for medical use in the late 1950s, but, the misuse of these compounds has increased among non-athletes to enhance physical performance [6,7]. The recommended therapeutic dose of Nandrolone for humans is 0.4 mg/kg/day, while doses used illegally commonly are up to 100 times the therapeutic dose [8]. However, due to adverse effects on cardiovascular, endocrine, reproductive and behavioral function, the rising Nandrolone abuse is a prevalent global problem [9,10]. As a result of the absence of a methyl group in the 19-position, Nandrolone displays less androgenic activity compared with testosterone [11]. However, due to its anabolic properties and the diminished ability to convert estrogen, Nandrolone is one of the most frequently abused AASs [12,13].

In this paper, we systematically reviewed experimental studies in order to determine whether is the possible relationship between

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Nandrolone exposure and behavioral and cognitive function in animal models.

1.1. Nandrolone metabolism

The half-life of Nandrolone administered by intramuscular injection is approximately 6 to 12 days. The mean half-life for release of the ester from the depot into the general circulation was 6 days, whereas the mean half-life for the combined processes of hydrolysis of ND and elimination of free Nandrolone was only 4.3 h [14]. The metabolism of Nandrolone occurs in the liver and is very similar to that of testosterone. Similar to testosterone, in specific tissues including, the prostate gland, liver, skin, hair follicles and brain, 5α-reductase will reduce the C-4,5 double bond of Nandrolone, yielding low-affinity androgenic receptor (AR) ligand dihydroNandrolone (DHN) [11]. However, DHN is less androgenic than Nandrolone as opposed to the relationship between testosterone and dihydrotestosterone [11,15]. Also the aromatization of Nandrolone to the estradiol-a ligand of the estrogen receptors- occurs similar to testosterone, but to a lesser extent than that of testosterone (only about 20% of that of testosterone or possibly even lesser) [11,16].

1.2. Mechanism of action: genomic and non-genomic pathway

Nandrolone is an agonist of the androgen receptors. The anabolic androgenic effects of Nandrolone are related to the AR-signaling action. There are three main action mechanisms: (1) direct interaction with AR; (2) through DHN produced by the action of 5- a-reductase, and (3) through estrogen receptors by estradiol produced by aromatase [17]. Previous studies have indicated that AASs, such as Nandrolone have a high affinity for the ARs [18]. In genomic mechanisms, steroid hormones mediate their effects through the activation of specific intracellular androgen receptors that act as a transcription factor. In this regard, after translocation into the cytoplasm, steroid hormone binds to and activates the androgen receptor. The bound steroid receptors act as transcription factors and fixe the hormone response element at DNA, where they activate or silence the expression of genes and subsequent protein synthesis [19,20].

Several reports have suggested that in addition to the genomic effect of steroid hormones through intracellular ARs, they have non-genomic action, as well. Non-genomic steroid function involves the rapid induction of conventional second messenger signal transduction cascades [21,22]. Accordingly, androgen interacts with a membrane-associated androgen receptor leading to the activation of L-type calcium channels and phospholipase C through an inhibitory G-protein. The resulted increases in intracellular calcium can activate protein kinase C, calmodulin and RAS/MEK/ERK pathway, finally affecting gene transcription [23].

1.3. Administration pattern

AASs are typically administered via the intramuscular or subcutaneous route, by pellet subcutaneous implantation, or by application on the skin [24]. Some indices are used to investigate the effects of Nandrolone on brain functions. AAS should be injected directly into the brain, while in most studies, Nandrolone is administrated via subcutaneous (s.c) or intramuscular (i.m) injections. In some experiments, the direct effect of Nandrolone on brain functions was examined by intracerebroventricular (i.c.v) [25-27] and intrahippocampal injections [28].

2. Methods

2.1. Search strategy

The Current systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [29]. Three databases were searched systematically, including PubMed, Embase, and ScienceDirect. Searching was conducted for studies published from 2000 to 2020. The used keywords were Nandrolone AND Cognition, Nandrolone AND Learning, Nandrolone AND Memory, Nandrolone AND (Synaptic plasticity or Hippocampal synaptic plasticity), Nandrolone AND (Aggression or Aggressive-like behavior), Nandrolone AND (Anxiety or Anxiety-like behavior), Nandrolone AND (Depression or Depressive-like behavior). Then, the records were imported and de-duplicated in EndNote.

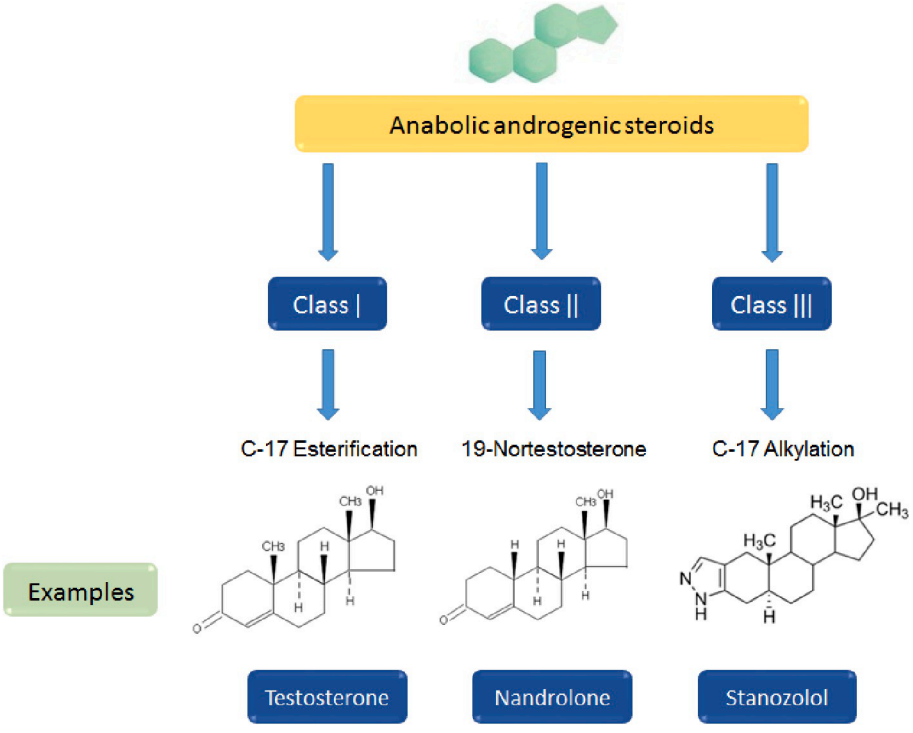

Fig. 1. The classification of anabolic androgenic steroids.

2.2. Eligibility criteria

In the first screening stage, based on titles and abstracts, the general inclusion criteria were articles published in the English language, studies on animal species, and original articles. Therefore, articles with no English full-text, clinical trials, and not original primary studies (e.g., review articles, editorials, conference abstracts, and case reports) were excluded.

In the second stage, full texts of articles were screened by authors to confirm studies eligible for inclusion criteria. In this step, unrelated articles and studies using mixed Nandrolone and other ASSs were excluded.

Fig. 3 shows the exclusion criteria used to select 33 qualified papers from the 2498 sources found.

3. Results

The results obtained from animal experiments reveal that Nandrolone is able to cause cognitive and behavioral effects, a graphical representation is displayed in Fig. 4. Of the 33 cases, 32 (96.97%) were males while only 1 (3.03%) were females and male.

3.1. Spatial memory

Of the 33 selected articles, 8 reported studies were related to spatial memory, all of which were related to males (6 adults, 2 immature). Table 1 summarizes animal experiments that evaluated the effect of Nandrolone exposure on spatial ability.

The study carried out by Salimi et al. showed that sub-chronic i.c.v. microinjection of ND improves spatial learning and memory of adolescent male rats and castration could abolish the ND-induced effect on spatial ability. This study is evidence supporting a positive correlation between ND and spatial ability [26]. In contrast, most studies suggest that the acute and chronic treatment with Nandrolone impaired spatial learning and retention of spatial information in adolescent and adult animals. El-Shamarka et al. investigated the effects of Nandrolone and cannabis (Can), alone and in combination, on spatial memory in adolescent male rats. Administration of Nandrolone (15 mg/kg, s.c.) once daily for one month, induced spatial learning and memory deficits in rats in the Morris water maze (MWM) test [30]. Also reported that, intrahippocampal injection of ND impaired spatial learning and memory functions by blocking androgen receptors [28].

In the study on adult male rats, it was confirmed that Nandrolone induces hyperlocomotion and spatial memory impairment [31]. In line with these findings Magnusson et al. have shown that subcutaneous (s.c.) injection of ND (15 mg/kg) in male rats leads to an impairment in MWM performance [32]. In another study, the effect of voluntary exercise on improving the cognitive deficits induced by chronic administration of ND and the effect of ND and voluntary exercise on hippocampal brain-derived neurotrophic factor (BDNF) levels were investigated. The results of this study indicated that voluntary exercise is unable to abolish the disrupting effect of ND on cognitive functions [33]. On the other hand, some investigators established no association between spatial ability and Nandrolone administration [34,35].

3.2. Avoidance memory

Of the 33 selected articles, 2 reported studies were related to avoidance memory, both of which were related to immature males as shown in Table 2.

The disrupting effect of Nandrolone supplementation on avoidance memory was documented in male rats. Zarei et al. [27] studied the effect of i.c.v microinjection of ND on passive avoidance memory (PAM) and CA1 synaptic plasticity. The results of this study showed that a single dose of ND could affect all stages of PAL, while its effects were more potent on retrieval. Also, in other study reported that ND reduces the retrieval of passive avoidance memory [25].

3.3. Hippocampal synaptic plasticity

Of the 33 selected articles, 11 studies reported information on synaptic plasticity, while 11 studies reported evidence on males (7 adults, 3 immature) and 1 studies reported evidence on adult male and female. Table 3 summarizes the animal studies that focused on the relationship between Nandrolone exposure and synaptic plasticity.

It has been reported that acute ND (0.6 and 3.6 μM/L) application impairs CA1 hippocampal synaptic plasticity and it can cancel the effect of HFS on fEPSP-LTP induction in adolescent male rats [27]. In addition,

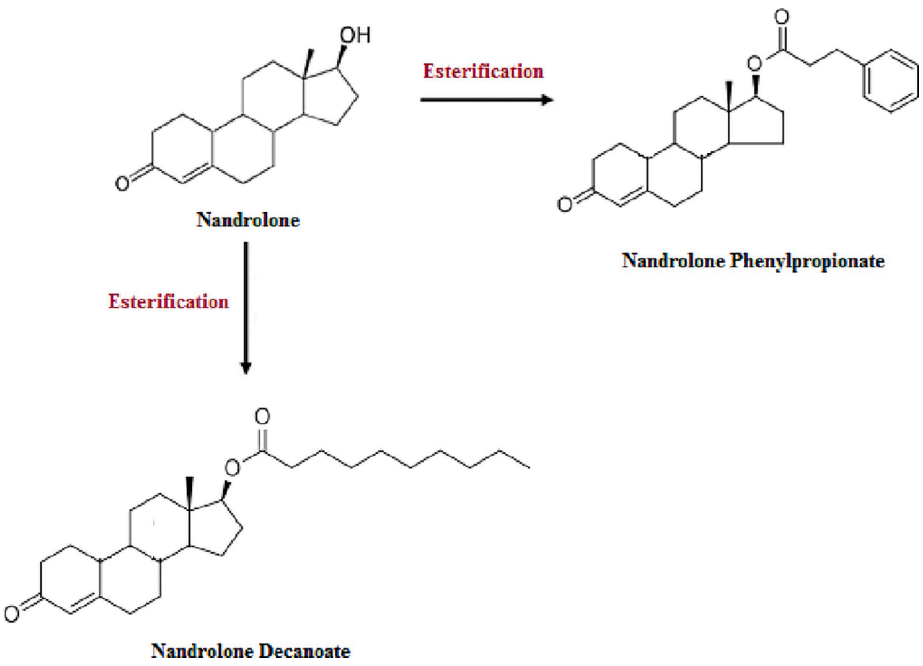

Fig. 2. Chemical structure of Nandrolone, Nandrolone decanoate and Nandrolone phenylpropionate.

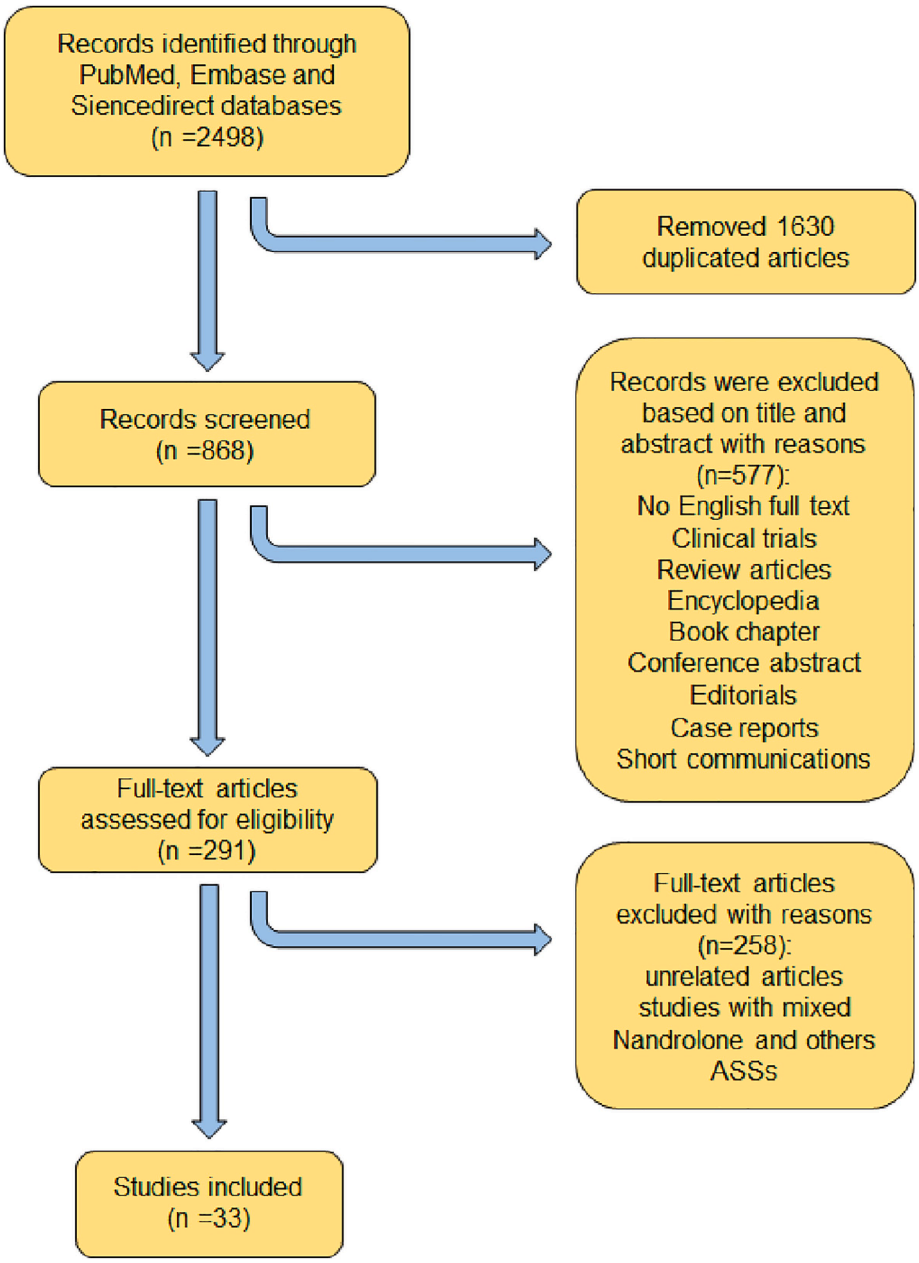

Fig. 3. The literature research strategy.

Moradpour et al. [25] indicated that ND administration impairs hippocampal synaptic plasticity. In contrast, the results of the study by salimi et al. showed that sub-chronic administration of ND improved CA1 hippocampal synaptic plasticity, but castration could abolish ND-induced synaptic plasticity improvement [26].

3.4. Aggressive behavior

Of the 33 selected articles, 11 reported studies were related to aggressive behavior, all of which were related to males (8 adults, 3 immature) as shown in table 4.

It has been reported that Nandrolone administration leads to an enhancement in the level of defensive aggression and irritability in adolescent and adult male rats [30,36]. Also, ND-injected adult male mic displayed aggressive behavior [37]. In line with these results, Farrell and McGinnis revealed that ND increased tail pinch-induced aggression in pubertal male rats [38]. Steensland et al. investigated how ND affects social interactions (with a focus on aggression and fear-related behaviors) of pair-housed rats, showing that the dominant ND-pretreated rats spent more time on highly aggressive behaviors than the dominant placebo-treated rats and the probability for highly aggressive behaviors was maintained for the ND-treated rats throughout the study [39]. In addition, in another study, amphetamine-induced aggression was enhanced in ND-pre-treated animals after 3 weeks of recovery, suggesting that ND induces long-lasting changes in the behavioral response to amphetamine pre-treatment [40].

Conversely, some studies found no association between Nandrolone exposure and aggressive behavior in pubertal and adult male rats [41-43].

3.5. Anxiety

Of the 33 selected articles, 8 reported studies were related to anxiety-like behavior, all of which were related to males (7 adults, 1 immature) as shown in table 5.

AAS exposure produces variable effects on anxiety-like responses in

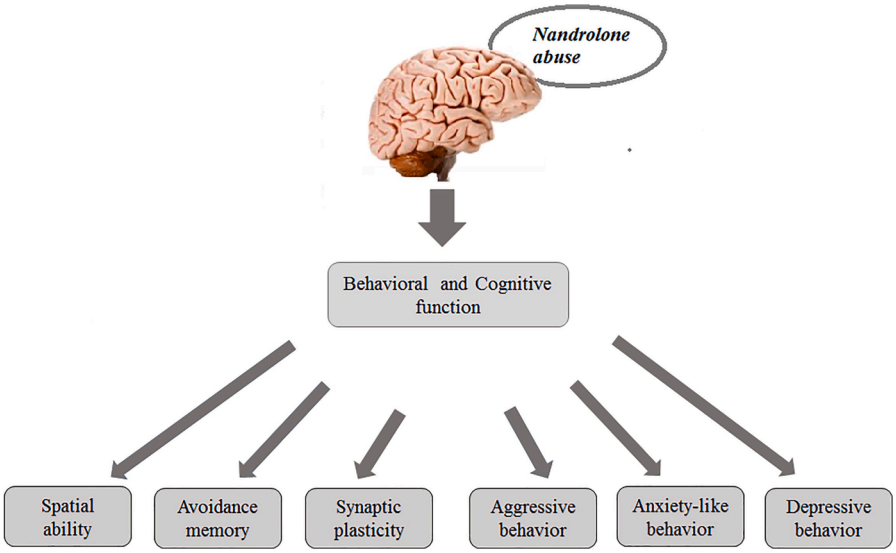

Fig. 4. Behavioral and cognitive functions changes induced by Nandrolone abuse.

Table 1
Summary of animal studies evaluating the effects of Nandrolone on spatial ability.

References	Main objective	Dosage and drug route	Animal	Outcome
Carteri et al., 2019	ND and T impair synaptic and extrasynaptic mitochondrial Ca2 + handling	ND, 15 mg/kg, s.c., daily for 19-days	Adult male mice	ND did not impair memory performance on MWM
Ahmed and El-Awdan, 2015	The possible protective effects of lipoic acid and/or pentoxifylline against ND	ND, 15 mg/kg, s.c., every third day for 30 days	Adult male rats	Nandrolone induced memory impairment in MWM task
Karamian et al., 2014	Acute effect of ND on spatial learning and memory	Intra-hippocampal injection of ND	Adult male rats	ND impaired spatial learning and memory in 8-arm radial maze
Grönbladh et al., 2013	The effect of GH on learning and memory in intact rats pretreated with the ND	ND, 15 mg/kg, s.c., every third day for 3 weeks	Adult male rats	The rats treated with ND did not exhibit any pronounced alteration in spatial memory in the MWM
Tanehkar et al., 2012	Whether voluntary exercise would improve the cognitive deficits induced by chronic administration of ND	ND, 15 mg/kg, s.c., every third day for 29 days	Adult male rats	Voluntary exercise is unable to improve the disruption of cognitive function by ND
Magnusson et al., 2009	Chronic treatment with ND affects spatial learning	ND, 15 mg/kg, s.c., every third day	Adult male rats	ND impairs memory function
El-Shamarka et al., 2020	Neurotoxic effects of Nandrolone and Cannabis, alone and in combination	ND, 15 mg/kg, s.c., once daily for one month	Adolescent male rats	Nandrolone induced spatial learning and memory deficits in the MWM test
Salimi et al., 2019	The effect of ND on spatial localization and synaptic plasticity	i.c.v. microinjection of ND (10, 30 and 60 μg), once daily for 4 days	Adolescent male rats	ND improved spatial learning

Table 2
Summary of animal studies evaluating the effects of Nandrolone on avoidance memory.

References	Main objective	Dosage and drug route	Animal	Outcome
Zarei et al., 2019	The acute effect of ND on PAL and CA1 synaptic plasticity	ND, 73, 146, or 219 mM, i.c.v., 30 min before training and retention test and after training	Adolescent male rats	Single dose of ND could affect all stages of PAL, its effects were more potent on retrieval
Moradpour et al., 2019	The role of Calcineurin in synaptic plasticity and memory storage impairment in ND administrated rats	ND, 100 μg/rat, i.c.v., before retention test	Adolescent male rats	ND may induce impairing effects on PAL memory storage through changes in the function of the Calcineurin

animal models. In the study carried out by El-Shamarka et al., the administration of Nandrolone to adolescent male rats produced a significant increase in anxiety-like behavior in the EPM test [30]. It has been indicated that Nandrolone administration elevated anxiety levels in adult male mice [37] and rats [44].

Rainer et al. clarified that prolonged Nandrolone exposure during adolescence induced anxiety-related behaviors during adulthood [45].

According to a study performed by Kouvelas et al., high doses of ND reduced anxiety in rats via direct activation of central ARs and not through secondary afferent stimuli evoked by peripheral actions of ND [46].

Some studies have shown no effects after chronic Nandrolone treatment in adult male mice [47] and rats [48].

3.6. Depression

Of the 33 selected articles, 6 reported studies were related to depression, all of which were related to adult males as shown in Table 6.

Depression is the second most common adverse effect in individuals who use supraphysiological doses of AASs [49].

Cattelan Souza et al. have reported that chronic administration of ND induced depressive-like behaviors [50]. Matrisciano et al. described

Table3
Summary of animal studies evaluating the effects of Nandrolone on synaptic plasticity.

References	Main objective	Dosage and drug route	Animal	Outcome
Rossbach et al., 2007	The impact of high doses of AAS on synaptic correlates	ND, 15 mg/kg, i.m., either as a single dose or daily over 2 weeks	Adult male rats	ND elicits phosphorylation of both NMDAR and ERK1/2
Elfverson et al., 2011	Further explore the mechanisms underlying Nandrolone-induced effects	ND, 15 mg/kg, s.c., every third day, for 14 day	Adult male rats	ND alters neurosteroid action at the sigma-1 receptor but not at the sigma-2 or NMDA receptors
Gomes et al., 2014	The effects of ND during a strength exercise on cell proliferation, apoptotic status and BDNF expression	4 weeks of progressive strength exercise with or without daily doses (5.0 mg/kg, SC) of ND	Adult male rats	Did not significantly modify BDNF and Pro-BDNF expression in the hippocampus
Rossbach et al., 2007	The impact of high doses of AAS on synaptic correlates	ND, 15 mg/kg, i.m., either as a single dose or daily over 2 weeks	Adult male rats	Did not detect any changes in BDNF expression
Matrisciano et al., 2010	The association between AAS abuse and depression	ND, 5 mg/kg, s.c., once a day for 28 days	Adult male rats	Reduction in BDNF expression in the hippocampus and prefrontal cortex
Tanehkar et al., 2013	The effects of ND and voluntary exercise on hippocampal BDNF levels	ND, 15 mg/kg, s.c., every third day for 15 days	Adult male rats	ND enhanced expression of BDNF
Tugyan et al., 2013	The neuroprotective effects of EPO in brain damage due to ND	ND, 10 mg/kg/ week, 8 weeks	Adult male rats	Significant reduction in cell proliferation, neurogenesis in hippocampus
Zarei et al., 2019	The acute effect of ND on PAL and CA1 synaptic plasticity	Hippocampal slices were perfused by ND 0.3, 0.6 and 3.6 μM/L	Adolescent male rats	ND application impair CA1 hippocampal synaptic plasticity
Moradpour et al., 2019	The role of Calcineurin in synaptic plasticity and memory storage impairment in ND administrated rats	Hippocampal slices were perfused by ND (0.6 μM/L) or ND plus Tacrolimus	Adolescent male rats	ND may induce impairing effects on synaptic plasticity through changes in the function of the Calcineurin
Salami et al., 2019	The effect of ND on spatial localization and synaptic plasticity	i.c.v. microinjection of ND (10, 30 and 60 μg), once daily for 4 days	Adolescent male rats	ND improved hippocampal synaptic plasticity
Brännvall et al., 2005	The effects of the ND on rat neural stem cells	ND, 15 mg/kg, s.c., daily for 5 days	Male, female, and timed-pregnant embryonic day (E)15 rats	ND reduced the number of neurons in hippocampus

Table 4
Summary of animal studies evaluating the effects of Nandrolone on aggressive behavior.

References	Main objective	Dosage and drug route	Animal	Outcome
Ahmed and El-Awdan, 2015	The possible protective effects of lipoic acid and/or pentoxifylline against ND-induced neurobehavioral alterations	ND, 15 mg/kg, s.c., every third day for 30 days	Adult male rats	Nandrolone induced aggression in resident–intruder test
Kalinine et al., 2014	ND-induced aggressive behavior is interconnected with GLT-1 activity, glutamate levels and abnormal NMDAr responses	ND, 15 mg/kg, s.c., for 4, 11 and 19 days	Adult male mice	Long-term ND-induced aggressive behavior in the resident–intruder test
Galal et al., 2013	Possible interaction between ND and amino acids on behavior and neurotransmitters	ND, 10 mg/kg, s.c., once weekly for 8 wk	Adult male rats	ND increased defensive aggression
Steensland et al., 2005	The effect of amphetamine on defensive reactivity and defensive aggression after chronic AAS treatment	ND, 15 mg/kg, i.m., daily for 14 days	Adult male rats	Amphetamine-induced aggression was enhanced in ND-pre-treated animals after 3 weeks of recovery
Steensland et al., 2005	How ND affects social interactions (with focus on aggression and fear-related behaviors) of pair-housed rats	ND, 15 mg/kg/day or placebo for 21 days	Adult male rats	The dominant ND-pretreated rats spent more time on highly aggressive behaviors
Breuer et al., 2001	The effects of AASs on aggression under different social and environmental conditions	ND, 5 mg/kg, 5 times/ week, for 12 weeks	Adult male rats	Aggressive behavior in ND males were similar to controls
Ambar and Chiavegatto, 2009	The emotional behaviorsof mice receiving prolonged high doses of ND	ND, 15 mg/kg, s.c., once daily for 28 days	Adult male mic	ND injected mic displayed aggressive behavior
McGinnis et al., 2002	The effects of different AAS on intermale aggression	ND, 5 mg/kg, s.c., 5 days per week for 12 weeks	Adult male rats	Tail pinch did not increase aggression in ND treated males
El-Shamarka et al., 2020	Neurotoxic effects of Nandrolone and Cannabis, alone and in combination	Nandrolone, 15 mg/kg, s.c., once daily for one month	Adolescent male rats	Nandrolone induced a significant increase in defensive aggression and irritability
Farrell and McGinnis, 2004	Acute and long-term effects of AAS exposure during puberty on intermale aggression	ND, 5 mg/kg, s.c., 5 days per week for 5 weeks	Pubertal male rats	ND increased tail pinch-induced aggression
Farrell and McGinnis, 2003	The effects of T, ND, and stanozolol during puberty	ND, 5 mg/kg, s.c., 5 days per week for 5 weeks	Pubertal male rats	ND had no effect on aggressive behavior

increased immobility in Nandrolone-treated intact adult male rats in the forced swim test. This study revealed that repeated injections of Nandrolone at a dosing regimen equivalent to that usually taken by AAS abusers induce a depressive state [51].

Joksimovic et al. have shown that chronic treatment with ND at supraphysiological dose resulted in depressive-like behavior. The findings of the study carried out by Zotti et al. suggest that Nandrolone-treated adult male rats have a depression-related sign, such as anhedonia [48], whereas, Ambar and Chiavegatto, reported antidepressant effects of Nandrolone administration in adult male mice [37].

Rainer et al. showed that prolonged ND exposure during adolescence leads to depressive-like behaviors during adulthood [45].

4. Discussion

Several mechanisms are involved in Nandrolone adverse effects and need to be better elucidated. The hippocampus is a part of the limbic system that has a well-known role in cognitive aspects of the brain [52]. The role of androgens in cognitive performance associated with the hippocampus has been suggested. The hippocampal CA1 pyramidal cell layer contains a high density of the androgen receptors, indicating that there must be a relationship between androgens and memory

Table 5
Summary of animal studies evaluating the effects of Nandrolone on anxiety.

References	Main objective	Dosage and drug route	Animal	Outcome
Zotti et al., 2014	The effects of ND on emotional behavior and neurochemical brain alterations	ND, 5 mg/kg, s.c., once daily, 5 days per week for 4 weeks	Adult male rats	Nandrolone had no effects on anxiety
Ahmed and El-Awdan, 2015	The possible protective effects of lipoic acid and/or pentoxifylline against ND-induced neurobehavioral alterations	ND, 15 mg/kg, s.c., every third day for 30 days	Adult male rats	Nandrolone induced anxiety
Kouvelas et al., 2008	Chronic administration of high doses of AASs affect anxiety and clarify the mechanism of action of ND	ND, 15 mg/kg s.c., once daily for 6 week	Adult male rats	Chronic administration of high doses of ND induce anxiolytic-like behavior
Ambar and Chiavegatto, 2009	The emotional behaviors of mice receiving prolonged high doses of ND	ND, 15 mg/kg, s.c., once daily for 28 days	Adult male mic	ND administration elevated anxiety level
Celerier et al., 2006	Influence of the anabolic–androgenic steroid Nandrolone on cannabinoid dependence	Nandrolone, 15 mg/kg, i.m	Adult male mice	Nandrolone had no effects on anxiety
Rocha et al., 2007	The influence of ND on anxiety levels	ND, 5 mg/kg, two times per week, i.m. for 6 weeks	Adult male rats	ND administration elevated anxiety level
Rainer et al., 2014	The long-term behavioral and neurophysiological consequences of Nandrolone abuse during adolescence	ND, 15 mg/kg/day, i.m., 13 day	Adult male rats	ND exposure during adolescence induced anxiety during adulthood
El-Shamarka et al., 2020	Neurotoxic effects of Nan and Can, alone and in combination, in adolescent male rats	Nandrolone, 15 mg/kg, s.c., once daily for one month	Adolescent male rats	Nandrolone produced a significant increase in anxiety-like behavior in the EPM test

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Table 6
Summary of animal studies evaluating the effects of Nandrolone on depressive behavior.

References	Main objective	Dosage and drug route	Animal	Outcome
Cattelan Souza et al., 2020	The involvement of KP/IDO activation in depressive-like behavior induced by ND	ND, 10 mg/kg, s.c., 28 day	Adult male mice	ND induced depressive-like behavior
Matrisciano et al., 2015	Repeated AAS treatment causes antidepressant-reversible alterations	Nandrolone, 5 mg/kg, S.c. once a day for 28 days.	Adult male rats	Repeated injections of Nandrolone induces a depressive state
Joksimovic et al.., 2008	the effects of chronic ND administration on depressive state	ND, 20 mg/kg/weekly, s.c., once a week for 6 weeks	Adult male rats	Chronic treatment with ND in supraphysiological dose resulted in depressive-like behavior
Zotti et al., 2014	the effects of Nandrolone decanoate on emotional behavior and neurochemical brain alterations	ND, 5 mg/kg, s.c., once daily, 5 days per week for 4 weeks	Adult male rats	ND-treated rats have a depression-related sign
Ambar and Chiavegatto, 2009	The emotional behaviors of mice receiving prolonged high doses of ND	ND, 15 mg/kg, s.c., once daily for 28 days	Adult male mic	ND administration had an antidepressant effects
Rainer et al., 2014	The long-term behavioral and neurophysiological consequences of Nandrolone abuse during adolescence	ND, 15 mg/kg/day, i.m., 13 day	Adult male rats	ND exposure during adolescence leads to depressive like behaviors during adulthood

performance [53,54]. Recently, animal experiments were performed to confirm the effect of Nandrolone on memory and help us to reveal the mechanisms behind the correlation between Nandrolone abuse and memory performance. It has been clarified that Nandrolone affects hippocampal synaptic plasticity and increases the testosterone and concentration levels [26,27]. On the other hand, pre-administration of AR antagonists could nullify the Nandrolone-induced reduction in the memory and hippocampal synaptic plasticity [27,55]. Together, these results indicate that possibly the effect of Nandrolone on memory arising from the alterations of hippocampal synaptic plasticity and/or directly through ARs and indirectly through alterations in plasma levels of testosterone and corticosterone. It can also be concluded that at least some effects of Nandrolone on memory may be induced through changes in gonadal hormones. In the study by Moradpour et al., the role of Calcineurin in synaptic plasticity and memory storage impairment in ND administrated adolescent male rats was evaluated, indicating that ND may induce impairing effects on hippocampal area CA1 plasticity and memory storage through changes in the function of the Calcineurin [25].

In a study on adult male rats established that the effect of Nandrolone were accompanied by several biochemical changes, including altered levels of brain monoamines, GABA, and acetylcholine [31], and also increased prodynorphin mRNA levels in the hippocampus observed in the ND treated animals could be one of the mechanisms of the ND-induced effects on cognition [32]. Additionally, ND administration enhanced the effect of exercise on BDNF levels. Therefore, increased levels of BDNF may play a role in ND-induced impairments in learning and memory [33]. Although further studies need to be carried out to investigate the effect of Nandrolone on the levels of mature and pro-BDNF, as they have distinct effects (pro-neurogenic and apoptotic effects, respectively).

Synaptic plasticity is structural changes in neurons and synapses that occur in certain brain structures particularly in the hippocampal excitatory synapses. It has been also established that long-term potentiation (LTP) and long-term depression (LTD) of the CA1 area of the hippocampus are underlying mechanisms [56]. Sex steroids affect LTP through structural and functional plasticity and synaptic regeneration [57,58].

In recent years, it has been hypothesized that non-classical effects of Nandrolone and other ASSs on CNS are mediated by interactions with membrane-bound receptors, such as the glutamate receptor *N*-methyl-D-aspartate subtype (NMDAR) [59,60] and the sigma-1 receptor [61,62]. In addition, there is now undoubted evidence that many forms of synaptic plasticity require ERK activation [63].

The NMDA receptor plays a critical role in LTP and LTD [64]. Phosphorylation of synaptic proteins particularly NMDAR regulates changes in synaptic strength and, in the hippocampus the activity of this protein is regulated by protein kinases that are closely associated with the formation of LTP and LTD [65]. It also has been suggested that sigma receptors (I and II) are involved in the development of cognitive function [66]. In order to investigate the mechanisms by which Nandrolone elicit their effects on CNS, Rossbach et al. have shown that a single high dose of the ND induces phosphorylation of both NMDAR and ERK1/2 in hippocampal synaptoneurosomes [67]. Also, Elfverson et al. demonstrated that chronic treatment of male rats with Nandrolone changes the

neurosteroids target on the sigma-1 receptor, but not the putative high-affinity neurosteroid sites on the NMDA receptor NR2B subunit [68].

The expression of BDNF is necessary for memory formation and synaptic plasticity [69,70] that is also altered by AASs. Matrisciano et al. (2010) reported a substantial decrease in BDNF expression in the hippocampus of adult male rats administered by ND [51]. On the other hand, Rossbach et al. (2007), observed no changes in BDNF expression in hippocampal synaptoneurosomes of rats administrated whit ND [67], also has been shown that chronic ND treatment did not significantly modify BDNF and Pro-BDNF expression in the hippocampus [71]. In contrast to these findings, another examination showed an enhanced expression of BDNF after ND injections in adult male rats [33].

Being exposed to high levels of the AAS ND resulted in a significant reduction in cell proliferation, neurogenesis, and the number of neurons in the hippocampus [72,73], leading to deficiency in the hippocampal synaptic plasticity.

The most common behavioral adverse effects of AAS abuse is increased aggression in adolescent [74,75] and adult peoples [76,77]. Several experiments have been conducted to clarify the mechanisms involved in aggressive behavior changes following exposure to AASs. In the study by Ahmed and El-Awdan, Nandrolone induced aggressive behavior in male rats via re-balance of brain neurotransmitters, up-regulation of Nrf2/HO1 pathway, and down-regulation of TNFR1 expression [31]. Also, long-term ND-induced aggressive behavior is associated with decreased extracellular glutamate clearance and an increase in the glutamate levels mediating NMDAR hyperexcitability, emphasizing the role of this receptor in mediating the mechanisms of aggression [78].

Nandrolone induced anxiety by several biochemical alterations in the brain, such as re-balance of brain neurotransmitters, up-regulation of Nrf2/HO1 pathway, down-regulation of TNFR1, and acetylcholine receptor expression [31]. Rainer et al. reported that prolonged ND exposure leads to depressive-like behaviors by decreased serotonergic activity and increased noradrenergic neurotransmission [45].

Cattelan Souza et al. have reported that Nandrolone induced depressive-like behaviors are accompanied by neurotoxic effects, such as a reduction in neurotrophin levels, 5-HT dysfunction, and inhibition of NA+, K+-ATPase in the hippocampus, striatum, and prefrontal cortex of mice [50]. Also, the findings of the study carried out by Joksimovic et al. showed that ND treatment resulted in a decrease in neuropeptide Y (NPY) content both in the blood and in the hippocampus, indicating that alterations in both blood and hippocampal NPY contents may underlie the changes in depressive state in male rats [79]. Also, another study suggested that this altered emotional profile is correlated with both a decrease in serotonergic activity and an increase in noradrenergic neurotransmission [45].

5. Conclusion

Even though the use of Nandrolone for medical purposes is relatively safe, it can be harmful to health and cause side effects if used improperly. Many studies have confirmed the side effects of Nandrolone abuse on the liver, kidney, cardiovascular, reproductive, musculoskeletal and endocrine systems. In addition to the general adverse effects of Nandrolone, on sexual functions, a large number of experiments have reported that administration of Nandrolone has an adverse effect on behavioral and cognitive functions.

In a systematic review of the literature on online resources, the outcomes obtained from animal experiments agrees on the fact that Nandrolone can affect spatial ability, passive avoidance memory and hippocampal synaptic plasticity. Also, the experimental results clarified that Nandrolone exposure produces variable effects on behavioral function such as aggressive behavior, depression and anxiety-like behavior.

However, despite decades of research on the relationship between Nandrolone and cognitive function, the achieved results are complex and contradictory. Some investigators have reported that treatment with Nandrolone impaired cognitive function. In contrast, some others suggest a positive correlation or no association between Nandrolone and cognitive performance. There are similar results for the effect of Nandrolone on behavioral performance. These discrepancies might be due to the differences in sex, age, dosage and treatment duration, and administration route. However, based on the published literatures, the negative results are more common than the published positive ones.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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