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## RESEARCH ARTICLE

# Effective treatment and prevention of attempted suicide, anxiety, and aggressiveness with fluoxetine, despite proven use of androgenic anabolic steroids

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## Abstract

The treatment of a man who attempted suicide after experiencing symptoms of anxiety and aggressiveness associated with the use of androgenic-anabolic steroids (AAS) is described. This report includes 30 days of inpatient treatment and a 6-month follow-up. Regular use of fluoxetine apparently prevented the onset of anxiety, depression, aggressiveness, and suicide ideation, even with the concurrent use of AAS. The urinary concentration of androgens, metabolites of AAS, and fluoxetine were monitored through analysis of urinary samples by the Brazilian Laboratory of Doping Control. Our results are congruent with previous findings describing the risk of suicide prompted by AAS use as well as the efficacy of fluoxetine in the treatment of mood disorders associated with the use of anabolic steroids.

## KEYWORDS

anabolic androgenic steroids, androgens, attempted suicide, mass spectrometry, performance-enhancing drugs

## 1 | INTRODUCTION

The use of androgenic anabolic steroids (AAS) can increase the risk of symptoms of anxiety and aggressiveness (Hall et al., 2005; Pagonis et al., 2006; Piacentino et al., 2015; Pope et al., 2000).<sup>1-6</sup> Likewise, suicide has been reported as one of the most frequent causes of unnatural death of anabolic steroid users.<sup>7</sup> Although the management of several AAS-related disorders has been described,<sup>8</sup> reports of treatment and

the prevention of psychiatric symptoms concomitant to the detection of AAS and other drugs are scarce. To the best of our knowledge, a single case series<sup>9</sup> has reported the successful treatment of AAS-related withdrawal and depression in humans with fluoxetine. Similar responses were found in a controlled experiment using a mouse model.<sup>10</sup> We present the case of a 24-year-old male who attempted suicide following the use of AAS. The individual was also affected by depressive symptoms during a brief AAS withdrawal. These symptoms

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were successfully treated with fluoxetine. After discharge, the patient relapsed back into the use of AAS but did not present symptoms of anxiety, aggressiveness, or suicide ideation, if a regular intake of fluoxetine was maintained. The use of AAS and fluoxetine by the patient was monitored by analysis of urinary samples to minimize confounding factors related to the self-reported use of substances, such as memory and disclosure bias.<sup>11,12</sup> Naturalistic observation of AAS use, such as this study, is additionally challenged by the use of substances of unknown composition from illicit markets,<sup>13</sup> therefore highlighting the importance of complementing self-reported data with the analysis of biological samples.<sup>14</sup>

## 2 | MATERIALS AND METHODS

The patient's clinical records were reviewed and described by obtaining prior informed consent from the patient. A summary of interventions is described in the "Timeline" image presented in Figure 1.

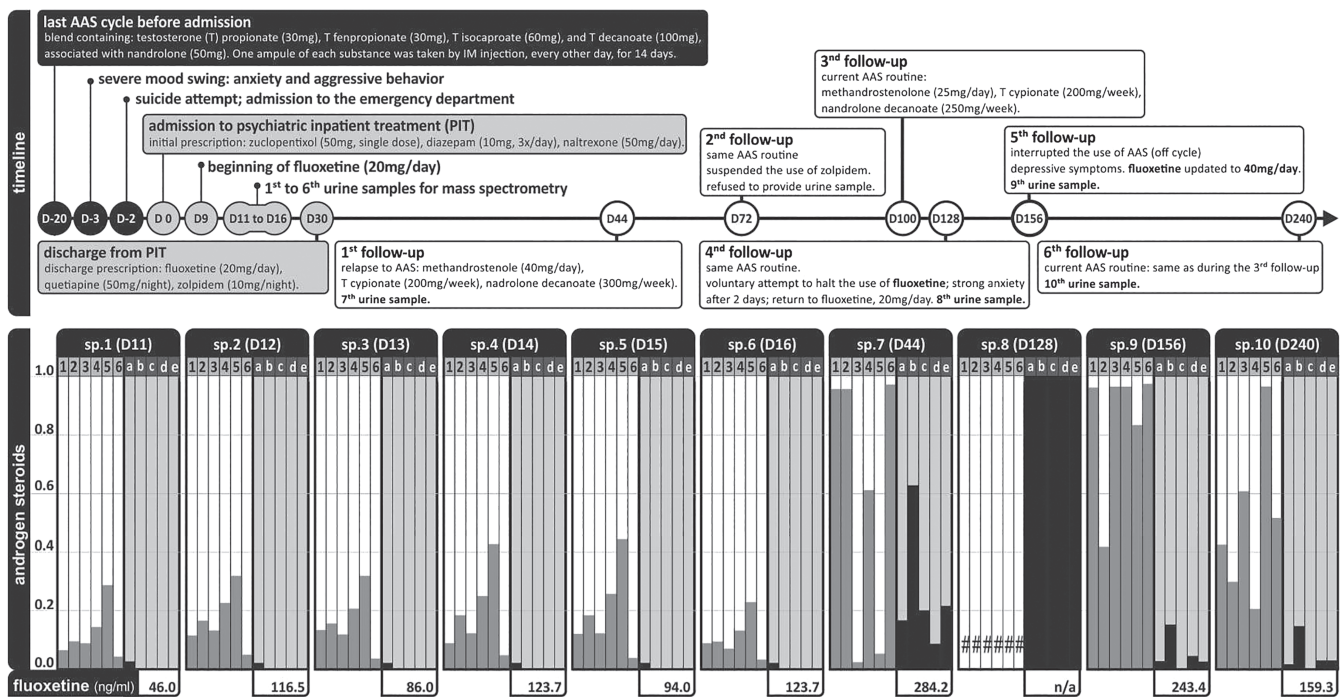
Toxicological screening on admission was performed by chromatographic immunoassay, using the AllTest Biotech rapid drug detection test (Hangzhou, China). One vial (30 mL) of urine was collected in the first 24 h of admission and three aliquots of 2 mL were dripped into the test device. A visual scale, showing the reaction of drug molecules with

colored antibodies, was used to provide a positive/negative recent use of the substances being screened. The following substances and periods of detectable use are informed by the manufacturer: cocaine, 3 days; cannabis, 1 to 13 days; amphetamine, 9 days; methamphetamine, 3 to 5 days; benzodiazepines, 3 to 7 days; opioids, 2 to 3 days; and 3,4-methylenedioxyamphetamine (MDMA), 2 to 3 days.

During inpatient treatment, urine samples were collected for 6 days. The patient provided four further samples during outpatient follow-up. Samples were analyzed for concentrations of fluoxetine, endogenous androgens, and the xenobiotic metabolites of AAS. The results and reference ranges are shown in Figure 1. Absolute values were normalized to a 0 to 1 scale so that parameters with distinct units and dispersions could be visualized in a single graph. The lower value detected of each androgen and metabolite corresponds to 0 in the graph, and the higher value corresponds to 1. A complete list of urinary concentrations of androgens, metabolites and fluoxetine can be found at Supporting Information.

The urine sample preparation was based on enzymatic hydrolysis and liquid-liquid extraction of AAS. Aliquots of 2 mL urine samples were spiked with 40  $\mu$ L of internal standard (Table 1).

During the initial testing procedure (screening), the steroid profile was estimated by single point calibration. Calibration samples, ie, quality control of endogenous steroids (CQENDO) were prepared by spiking synthetic urine with endogenous steroids standards in their free



**FIGURE 1** Timeline and concentrations of androgen steroids and fluoxetine detected in urine samples. The lower value detected of each androgen and metabolite corresponds to 0 in the graph, and the higher value corresponds to 1. Sp, Sample number, as referred in the timeline; PIT, psychiatric inpatient treatment. Androgen steroids: (1) androsterone; (2) etiocholanolone; (3) 5 $\alpha$ -androstane, 3 $\alpha$ -17 $\beta$ , diol; (4) 5 $\beta$ -androstane, 3 $\alpha$ -17 $\beta$ , diol; (5) epitestosterone; (6) testosterone. #: Values out of linear range. (a) Nandrolone; (b) Boldenone; (c) 1-testosterone; (d) Methandienone; (e) Drostanolone. The analysis of urinary concentration of fluoxetine on sp.8 (D128) was not performed due to insufficient amounts of urine



**TABLE 1** Internal standard composition [Colour table can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

Deuterated steroid	Concentration (ng/ $\mu$ L)
Epitestosterone-D3	0.75
Testosterone-D3	3.0
Ethiocolanolone-D4	25
Androsterone glucuronide-D5	25
5 $\alpha$ -Androstanediol-D5	4.0
5 $\beta$ -Androstanediol-D4	9.0

form. Nominal final concentrations of the compounds for the CQENDO samples are presented in Table 2.

The pH was adjusted with 750  $\mu$ L of 0.8 M phosphate buffer, and 50  $\mu$ L of  $\beta$ -glucuronidase obtained from *Escherichia coli* (*E. coli*) was added. It was incubated at 50°C for 1 hour, and then 500  $\mu$ L of aqueous buffer solution containing K<sub>2</sub>CO<sub>3</sub>/KHCO<sub>3</sub> 20% (w/w) and 4 mL of methyl tert-butyl ether (TBME) was added. The mixture was stirred for 5 min and centrifuged at 3000 rpm for 5 min. After phase separation, the organic phase was evaporated to dryness under nitrogen and dried in a vacuum oven for 30 min at room temperature. Finally, the residue was derivatized with 100  $\mu$ L of N-methyl-N-(trimethylsilyl) trifluoroacetamide (MSTFA)-NH<sub>4</sub>I-2-mercaptoethanol (1000:2:6, v/w/v) 60°C for 20 minutes. Aliquots of 2  $\mu$ L were injected in splitless mode into the triple quadrupole system (GC-QqQ) operated in multiple reaction monitoring mode. The analysis was performed using a gas chromatograph (GC) Trace 1310 (Thermo Scientific) and interfaced with a mass spectrometer TSQ 8000 (Thermo Scientific), column 100% methylpolysiloxane phase (17 m  $\times$  0.20 mm  $\times$  0.11  $\mu$ m).

List of the reagents: methanol (pesticide grade), ethyl acetate (GC grade), acetone (GC grade), and tert butyl methyl ether (GC grade) were purchased from Tedia (Fairfield, OH, USA). N-Methyl-N-(trimethylsilyl)-trifluoroacetamide, 2-mercaptoethanol, and ammonium iodide were purchased from Sigma Aldrich (St Louis, MO,

**TABLE 2** CQENDO composition [Colour table can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

Endogenous steroid	Concentration (ng/ $\mu$ L)
11-Cetoethiocolanolone	1000
16-Androstenol	500
Tetrahydrocortisol	1000
Pregnanediol	1000
Prasterone	400
Dihydrotestosterone	400
11 $\beta$ OH-Etiocholanolone	200
5 $\alpha$ -Androstanediol	180
5 $\beta$ -Androstanediol	80
Epitestosterone	40
Testosterone	40
Ethiocolanolone	2000
Androsterone	2000

USA). Sodium dihydrogen phosphate monohydrate, di-sodium hydrogen phosphate, potassium carbonate, and potassium hydrogen carbonate were purchased from Merck KGaA (Darmstadt, Germany).  $\beta$ -Glucuronidase from *E. coli* was purchased from Roche Diagnostics GmbH (Mannheim, Germany). Compressed helium (99.999% purity) and argon (99.999% purity) gases were purchased from White Martins (São Paulo, Brazil). All reference materials were purchased from the National Measurement Institute (Australia).

The GC electron impact source mass spectrometry (GC-EI-MS/MS) conditions were: oven temperature program 140 to 230°C at 40°C/min, 230 to 280°C at 3°C/min, 280 to 300°C and held at 300°C for 3 min. The transfer line was set to 300°C and the ion source was set to 320°C. Electron ionization was performed using electron energy of 70 eV.

The collision energies were optimized according to the software Auto SRM. The dwell time was set to reach ten points across the peak for the narrowest peak.

For liquid chromatography (LC), high-resolution mass spectrometry (LC-HRMS) conditions, and fluoxetine evaluation the LC separations were performed on Dionex UltiMate 3000 UHPLC system (ThermoScientific, using a Synchronis C 18 column (50  $\times$  2.1 mm  $\times$  1.7  $\mu$ m) maintained at 40°C. The mobile phase A (water, 0.1% formic acid and 5 mM ammonium formate) and mobile phase B (methanol and 0.1% formic acid) were employed in the following gradient of B mobile phase: 0 min, 5%; 0.3 min, 5%; 0.5 min, 10%; 1 min 25%; 6 min, 90%; 8 min, 100%; 9 min, 100%; 9.1 min, 5%; 11 min, 5%. The flow rate was 400  $\mu$ L/min and the injection volume was 10  $\mu$ L. For high resolution mass spectrometry analysis a QExactive<sup>TM</sup> Plus Orbitrap mass spectrometer (MS) (ThermoFisher Scientific, Bremen, Germany) was used in positive mode ionization. The mass detection range was m/z 100–900 in data dependent acquisition mode for MS<sup>2</sup> fragmentation experiments. The automatic gain control (AGC) target was set to 1e6 and maximum ion time (IT) was set to 100 ms. The sheath gas flow rate and the auxiliary gas flow rate were set to 60 and 20 respectively, the spray voltage was 3.90 kV, the capillary temperature was 380°C, the S-lens radio frequency (RF) level 80, the auxiliary gas heater temperature was 380°C.

Fluoxetine could be detected in  $t_R = 6.15$  min with the exact mass equal to m/z 310.14120. As internal standard 7-propilteofiline was used. It is detected at  $t_R = 3.75$  min and the monitored transition is m/z 372  $\rightarrow$  m/z 210. This internal standard in 50 ng/mL was used to infer the concentration of fluoxetine in patient urine samples.

The data were evaluated using Thermo Fisher Scientific TraceFinder<sup>TM</sup> 3.2.512.0 software (Thermo Fisher Scientific, Waltham, MA, USA).

This study is registered at the Brazilian Committee for Ethics in Research under CAAE: 83109618.6.0000.5263.

### 3 | CASE DESCRIPTION

The patient identified as Mr Y was a 24-year-old man with a history of AAS use over the previous 6 years. According to the patient's

family members, he had a normal neuropsychological development and no record of alcohol abuse or consumption of illegal drugs. There was no history of relevant clinical disorders, surgeries, significant traumas, allergies, or diagnosed psychiatric disorders. As reported by his parents, Mr Y's behavior suddenly changed when he was 19 years old – the time when he started using AAS, as confirmed by the patient. From that moment on, Mr Y began to display a more aggressive, short-tempered behavior, every time he started a new routine of AAS, also known as a “cycle”. Mr Y confirmed that he had used different AAS in his life, including counterfeit compounds of unknown composition, but had not yet required assistance for any effects associated with the use of anabolic steroids. According to the patient, 20 days before admission into our medical service (henceforth referred to as D minus 20 or D-20), he started a 14-day AAS cycle with a substance known as “durateston”, containing 30 mg of testosterone propionate, 30 mg of testosterone fenpropionate, 60 mg of testosterone isocaproate, and 100 mg of testosterone decanoate.

Mr Y experienced episodes of mood swings with severe anxiety and aggressiveness on D-3, including threatening to kill his partner due to uncontrollable feelings of jealousy. On D-2, the patient ingested 20 mg of clonazepam and attempted suicide by hanging himself by the neck with a leather belt. Mr Y was found by his parents in the balcony of his apartment and taken to the emergency department (ED). There, he recovered consciousness and reacted aggressively to medical interventions until he was medicated with intramuscular (IM) injections of midazolam, haloperidol decanoate, promethazine, chlorpromazine, phenobarbital, and diazepam. Mr Y stayed at the ED for approximately 24 hours, and was transferred to the psychiatric facility where this study was conducted on D0 (day zero) for inpatient treatment. (See the Timeline in Figure 1 for details of pharmacological treatment and the use of substances informed by the patient).

On admission, a urine toxicological analysis was performed for screening of recent use of drugs, as described in the Methods section. This test showed solely the recent use of benzodiazepines, a result compatible with the drugs recently used by the patient. As the urine toxicological kit did not include screening for anabolic agents, these substances were tracked by applying the doping control analytical protocols described previously.

One week after admission, the patient remained in a depressive mood, reporting not remembering his suicide attempt or aggressive behavior. Fluoxetine (20 mg/day) was prescribed on D9 of inpatient treatment. A significant improvement in mood and disposition was observed on D16. Blood serum analysis on admission and 3 months after discharge revealed persistent hormone imbalance. Follicle-stimulating hormone (FSH) remained below 0.3 mIU/mL for both measures, luteinizing hormone (LH) remained below 0.12 mIU/mL, estradiol varied from 45.00 pg/dL to 75.81 pg/dL, prolactin ranged from 43.10 ng/mL to 17.27 ng/mL, and testosterone varied from 1352 ng/mL to 1500 ng/mL. As shown in Figure 1, urinary analysis revealed a tendency for regularization of androgen concentrations during inpatient treatment. For the duration of this report, the patient did not present health complications or symptoms, apart from those hereby described, that could have interfered in the study.

Mr Y was discharged from inpatient treatment 30 days after admission, with an alleged resolution to quit the use of AAS. The patient refused to attend meetings with a psychologist after discharge, but agreed to regular consultations with the first author, Dr Amaral. Despite continuous treatment and medical advice, the patient relapsed back into steroid use, as confirmed by urinary analysis. On the fourth follow-up consultation (D128), the use of AAS had raised all androgen concentrations above the 95% upper reference limit.<sup>15,16</sup> Mr Y informed us that he had voluntarily halted the use of fluoxetine, 14 days before this consultation because he believed the antidepressant was no longer necessary. However, the patient reported severe symptoms of anxiety, leading to our decision to initiate again treatment with fluoxetine, re-introducing the antidepressant in lower doses. After 4 weeks of 10 mg/day of fluoxetine, the patient reported only a minor improvement in mood, so the dose was increased to 20 mg/day with complete remission of depressive symptoms in the following 20 weeks. Despite all advice, Mr Y was unwilling to suspend the use of AAS, but adhered to the concurrent intake of fluoxetine. No further symptoms of anxiety, aggression, or suicide attempts occurred until the completion of this report, 240 days after admission.

## 4 | DISCUSSION

It is unusual that AAS users seek psychiatric help for steroid-related symptoms (<sup>17,18</sup>; Bates et al., 2019).<sup>19</sup> This case is not an exception, since the patient was admitted into treatment by his family after his suicide attempt. Although the patient has confirmed the long-term use of AAS, so establishing causality between the use of steroids and mood disorders, this case is compromised by the lack of a psychiatric assessment prior to the use of AAS. Nevertheless, the onset of aggressive symptoms immediately after an AAS cycle and the patient's emotional fluctuations during AAS cycles allow us to infer an association between the use of AAS and behavioral changes that culminated in a suicide attempt. Different metabolites of xenobiotic steroids for the patient were found in each mass spectrometric analysis, therefore hampering the identification of the specific AAS used during the period of the study.

When the patient was admitted for psychiatric treatment, biochemical analysis revealed a hormone imbalance compatible with the chronic use of exogenous testosterone, such as the suppression of gonadotropins.<sup>20</sup> Drugs administered prior to Mr Y's admission, namely the long-lasting haloperidol decanoate, are confounding factors for the initial response to medication. Notwithstanding, the response to fluoxetine was observed for more than 3 months after the use of haloperidol, as confirmed by chemical monitoring of the patient's urine samples.

Depressive mood was the most remarkable symptom during the post-acute phase of AAS intoxication. A short withdrawal was followed by a relapse into the use of AAS, but no symptoms of anxiety, aggressiveness, insomnia, or depressive mood were observed if a regular intake of fluoxetine was sustained. Another confounding

factor for the recurrence of symptoms was the abrupt discontinuation of fluoxetine, which can be associated with irritability and depressive symptoms.<sup>21</sup> Still, the lack of response to 10 mg of fluoxetine during the AAS cycles on follow-up support the hypothesis of a dose-related effect of fluoxetine in successfully treating and preventing the onset of AAS-triggered aggressiveness and anxiety in this patient, as well as depressive symptoms related to AAS withdrawal. Prior to this study, Malone and Dimeff<sup>9</sup> described the treatment of psychiatric symptoms of AAS with fluoxetine, in a case series of four patients. Similarly, Mr Y noted complete remission of depressive symptoms with a daily intake of a single dose of 20 mg of fluoxetine. Apparently, the antidepressant may have also prevented new episodes of anxiety and aggressiveness during the concurrent use of AAS, but controlled experiments with the concurrent use of these substances in humans are necessary to understand their interaction. Studies with animals exposed to AAS observed an effect of fluoxetine in reducing aggressiveness<sup>22</sup> and anxiety-like symptoms during AAS withdrawal.<sup>10</sup> Similar effects were reported when using the 5HT1A receptor agonist 8-OH-DPAT.<sup>23</sup> To the best of our knowledge, there are no reports of pharmaceutical interactions between fluoxetine and AAS. Besides, no association is observed between the treatment with fluoxetine and testosterone levels.<sup>24</sup> Regarding recommendations for treatment, it is important to highlight that AAS can trigger or aggravate the symptoms of mania and hypomania.<sup>24</sup> Since fluoxetine has the potential to induce mania in some patients,<sup>25</sup> this drug must be carefully monitored when prescribed to AAS users, namely in outpatient settings.

Underlying mechanisms of action of AAS on the serotonergic system in animals have been described by several authors,<sup>22,23,26–28</sup> and serotonin signaling is apparently involved in the anxiogenic and depressive effects observed during AAS withdrawal.<sup>29</sup> An increased risk of suicide in AAS users<sup>7</sup> seems to be related to the depressive and aggressive symptoms experienced by those patients.<sup>30,31</sup> This may be related to the effects of testosterone on the serotonergic pathways related to suicidality.<sup>32</sup> AAS also seem to decrease serotonergic activity in the basal forebrain and dorsal striatum. They also decrease 5HT1A receptors on the anterior hypothalamus and downregulate 5HT1B receptors in the globus pallidus and in the CA1 area of the hippocampus.<sup>22</sup> Therefore they affect the regions involved in the control of aggression. Another hypothesis is that AAS-related anxiety, aggressiveness, and depression are related to decreased synthesis of serotonin and increased cerebral levels of neuroactive kynurenines.<sup>33</sup>

The limitations of this study include the lack of access to the precise AAS composition and doses used by Mr Y. The main confounding factor is the patient's exposure to unknown steroids and drugs. The variety of AAS metabolites found in the urine samples precludes the identification of all the androgens used by the patient. Nevertheless, the analysis of a range of endogenous and xenobiotic AAS, as prescribed in doping control analysis protocols, gives a reasonable picture of the substances used by the patient for the duration of this study. Suggested improvements for future studies include a randomized and double-blinded controlled experiment, the provision of verified doses

of AAS, regular toxicological screening, and longitudinal psychometric evaluations.

## 5 | CONCLUSIONS

The onset of anxiety, aggressiveness, and a suicide attempt were observed following the use of AAS as well as depressive symptoms on AAS withdrawal, in congruence with previous reports. Fluoxetine was effective in treating AAS post-cycle depression in this patient, as well as preventing new episodes of aggressiveness or suicide attempts despite the patient exposure to subsequent doses of anabolic steroids. Drug interactions between AAS and fluoxetine must be monitored due to the risk of induction of mania presented by both substances. Controlled studies are needed to fully understand the mechanisms of fluoxetine effects over AAS-related psychiatric symptoms.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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