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Prevalence of antidepressants and biosimilars in elite sport

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The use of prescribed antidepressants by athletes has not been restricted in human sports since 2003, after the antidepressants bupropion and amineptine were removed from the list of prohibited substances. Recent awareness of antidepressants has been stimulated by reports from the media concerning possible misuse of antidepressants among healthy athletes.

The prevalence of antidepressants has been monitored over the past ten years with screening procedures routinely used by WADA-accredited laboratories. The growth in antidepressant use among athletes peaked in 2007 and 2008 after a modest increase over the first eight years of this survey. Pharmacy prescriptions for antidepressants in Germany did not show a correlated growth during this period. The increasing variety of antidepressant medications has led to a continued increase in the diversity of antidepressant substances used by athletes and the 'normal' population. The number of different sports affected by the presence of antidepressants has increased in the past decade, especially in endurance sports. The predominance of female antidepressant users in the normal population was reflected in the athletes' group. We concluded from our results that the development of antidepressant prevalence in elite sports did not correlate with that among the general public in Germany.

Keywords: antidepressant; doping; elite sport; gas chromatography/mass spectrometry; selective serotonin reuptake inhibitor

Introduction

The therapeutic use of antidepressants (ADs) has been confined to major depressive, dysthymic and bipolar disorders. Selected agents have also proved useful for the treatment of other disorders such as generalized anxiety, post-traumatic stress disorder, social phobia and bulimia nervosa.[1,2] These mental disorders result from complex and multi-factorial disharmony in social and chemical structures. More refined analysis of depression has led to two hypotheses on the causality of neuropathologies and mental illness:

- Depression arises from an imbalance in neurotransmitter amines (such as noradrenalin, serotonin, dopamine) in the brain.[3,4]
- Corticoid receptor signalling is impaired, resulting in increased production and secretion of corticotrophin-releasing hormone in various brain regions.[5] The subsequent long-term presence of the stress hormone hydrocortisone reinforces the pathogenesis of depression.

Most ADs interfere with the neuroamine mechanism in that they increase the concentration of neurotransmitter amines in the synaptic gap.[6] The introduction in the past decade of the selective serotonin reuptake inhibitors (SSRIs), including Prozac® and other ADs with atypical action mechanisms, has led to a significant increase in prescriptions for these drugs. Reasons for this might be the more acceptable side-effect profile of the new generation of ADs in contrast to the conventional tricyclic ADs (TCA), the expansion of indications and better acceptance and compliance by patients.[7] Modern ADs are characterized by their specific central receptor binding or target enzyme inhibition and can be divided into eight classes according to the site of action (Table 1).[8]

The efficacy and beneficial pharmacodynamics of ADs are controversial.[9–12] Although some ADs have proven their usefulness in therapy for different mental disorders, beneficial effects in healthy people have not been investigated so far. However, anecdotal reports[13,14] claim that ADs exhibit effects that might have an indirect positive influence on performance, including stimulating, euphoric, anxiolytic, antiemetic and self-esteem boosting properties. The frequency with which ADs, in particular SSRIs, have been mentioned and advertised in the media has led to the marketing of ADs as recreational drugs.

Antidepressant drugs have been uncovered in house searches, in which medical attendants of top-level cyclists and soccer players were involved. Replying to legal inquiries, cyclists confessed to regularly using ADs during international tour events to stimulate their motivation and to try to obtain a euphoric effect.[13] Performance-enhancing effects of AD biosimilars have recently been confirmed in a study on performance and thermoregulatory effects after chronic bupropion administration to cyclists.[15]

Sports authorities do not consistently regulate the use of ADs in sports. Before 2003 some ADs were prohibited in sports by the IOC regulations. The recent WADA doping list does not include ADs; only bupropion is still on WADA's monitoring list. In 2006 WADA added sibutramine, a drug affecting the serotonin and noradrenalin reuptake system, to the list of prohibited substances. Since 2009 it has been categorized under section S6b for specified stimulants. Sibutramine was also under consideration in the late 1980s.[16]

The aim of the present study was to monitor the prevalence of ADs in elite sports. Data from this survey include the identification and distribution of certain ADs as well as demographic charac-

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Table 1. Classification of modern antidepressants

Class	Examples of substances in class
SSRI Selective serotonin reuptake inhibitors	Citalopram, Escilatopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline
SNRI Selective noradrenalin reuptake inhibitors	Reboxetine
SSNRI Selective serotonin and noradrenalin reuptake inhibitors	Venlafaxine, Duloxetine, Sibutramine
NaSSA Noradrenaline and serotonin specific antidepressants (α_2-Antagonists)	Mirtazapine
NDRI Noradrenaline and dopamine reuptake inhibitors	Bupropion
SARI Serotonin antagonist and reuptake inhibitor	Trazodone
DSA Dual serotonergic antidepressant	Nefazodone
RIMA Reversible inhibitors of monoaminoxidase-A	Moclobemide

teristics such as gender, different sports and annual percentage changes over the last ten years analysed in our laboratory. These results were correlated with the increasing number of pharmacy prescriptions for ADs in Germany.[17]

Materials and Methods

All of the samples analysed were doping control samples. They were obtained from 178 different sports authorized by German and other international federations. In total, samples from 50 nations were included in the study, but predominantly samples originating from events in Germany and other European countries. Samples were collected in and out of competition. Gender distribution of male and female athletes was 68% and 21% respectively. Information on the athlete's sex was not provided for 11% of the samples. The 178 different sports were categorized into seven major sports groups: (1) endurance, (2) athletics, (3) power and strength, (4) team sports, (5) fighting, (6) disability sports, (7) miscellaneous. This classification was made by prioritizing specific characteristics of the sports. These characteristics were weighted in order to examine the 'true' nature of the sport. For example, soccer was classified as a team sport even though it has elements of athletics and endurance. Sports, in which an aerobic energy supply was essential (such as cycling, cross-country skiing and triathlon) were classified as endurance sports. The differentiation between athletics and endurance sports could only be made for those samples for which the specific discipline was known. That meant that samples from the International Association of Athletic Federations (IAAF) and the German Athletic Federation were allocated to athletics, unless information on the endurance character of the discipline was indicated.

Considering the age dependency of performance, particularity in the population studied (top level athletes), it was assumed that the majority of the athletes' population would be aged between 20 and 40 years. Because of the anonymous character of doping control forms, double counting of athletes selected more frequently for doping control cannot be excluded.

All samples underwent a validated routine screening procedure for the detection of unconjugated neutral or basic compounds. The sample preparation and analysis is described elsewhere.[18]

Briefly, 1-(N,N-diisopropylamino)-n-dodecane and approximately 3 g of sodium sulphate was added to 5 mL of urine. Analytes were extracted into *tert*-butylmethyl ether under alkaline conditions (pH 14) and analysis was performed on a combined system of gas chromatography-mass spectrometry and gas chromatography nitrogen-phosphorus detector (GC-MS/NPD). The discovery of an AD user was proved by the presence of the parent AD and/or by the presence of one or more metabolites.

Antidepressants and their metabolites were characterized by comparison of their electron ionization mass spectra (EI-MS) in the full-scan mode with EI mass spectral data from MS databases (such as AORC R.7a, Wiley) and from the literature.[19]

Results and Discussion

Although it should be recognized that the method used was not developed exclusively for the screening of ADs, it is suitable for the analysis of unconjugated basic and neutral compounds (such as ADs) in human urine. The method also enabled the detection of phase I metabolites.[20,21] Phase II metabolites, whose formation is well known from the literature,[22,23] were not detected by the method used. Nevertheless, from the number of different ADs it can be concluded that most ADs are, at least partially, excreted unconjugated and covered by the presented method. Figure 1 lists the chemical structures of the identified AD and related substances with known AD properties.

During the course of the survey, over the past ten years, a selection of 26 different substances with antidepressant properties were identified. From a total of 82 880 analysed samples, 258 (0.31%) were found to contain at least one AD. The percentage of AD users relative to the total number of analysed samples per year showed a sixfold increase from 1999 (0.10%) to 2008 (0.63%). The modest growth in AD use from 1999 to 2006 was followed by a rapid increase in 2007 and 2008, in which the percentage of AD positives more than doubled (Table 2). This was in contrast with the continuing linear growth of pharmacy prescriptions for ADs in Germany between 1999 and 2007 (Figure 2).

The growing variety of AD medications has led to an increasing number of different ADs used by athletes (three in 1999, 17 in 2008). The number of different sports concerned with ADs increased from five in 1999 to 22 in 2008 (Table 2). From 1999 to 2004 the use of ADs has apparently been restricted to specific sports showing a preference for endurance sports (Table 3). From 2005 the number of different sports concerned with ADs has continued to expand. Endurance sports are still characterized by considerable and regular AD use. Among the endurance athletes, cyclists have contributed as the major group. The high percentage of users performing in disability sports might be attributable to a general higher consumption of medicines in this group and/or the low number of tested disabled athletes and might therefore be overestimated.

Table 4 summarizes the detected AD substances and their chronology over the last ten years. Amitriptyline, citalopram and fluoxetine have been used over practically the entire period of the study, whereas no other AD was introduced to the sports world before 2001. In the past decade, fluoxetine (75 counts) was the most frequently used AD followed by citalopram (43 counts).

Figure 3 compares the mean annual percentage distribution of AD classes used by athletes from 1999–2008 to the percentage

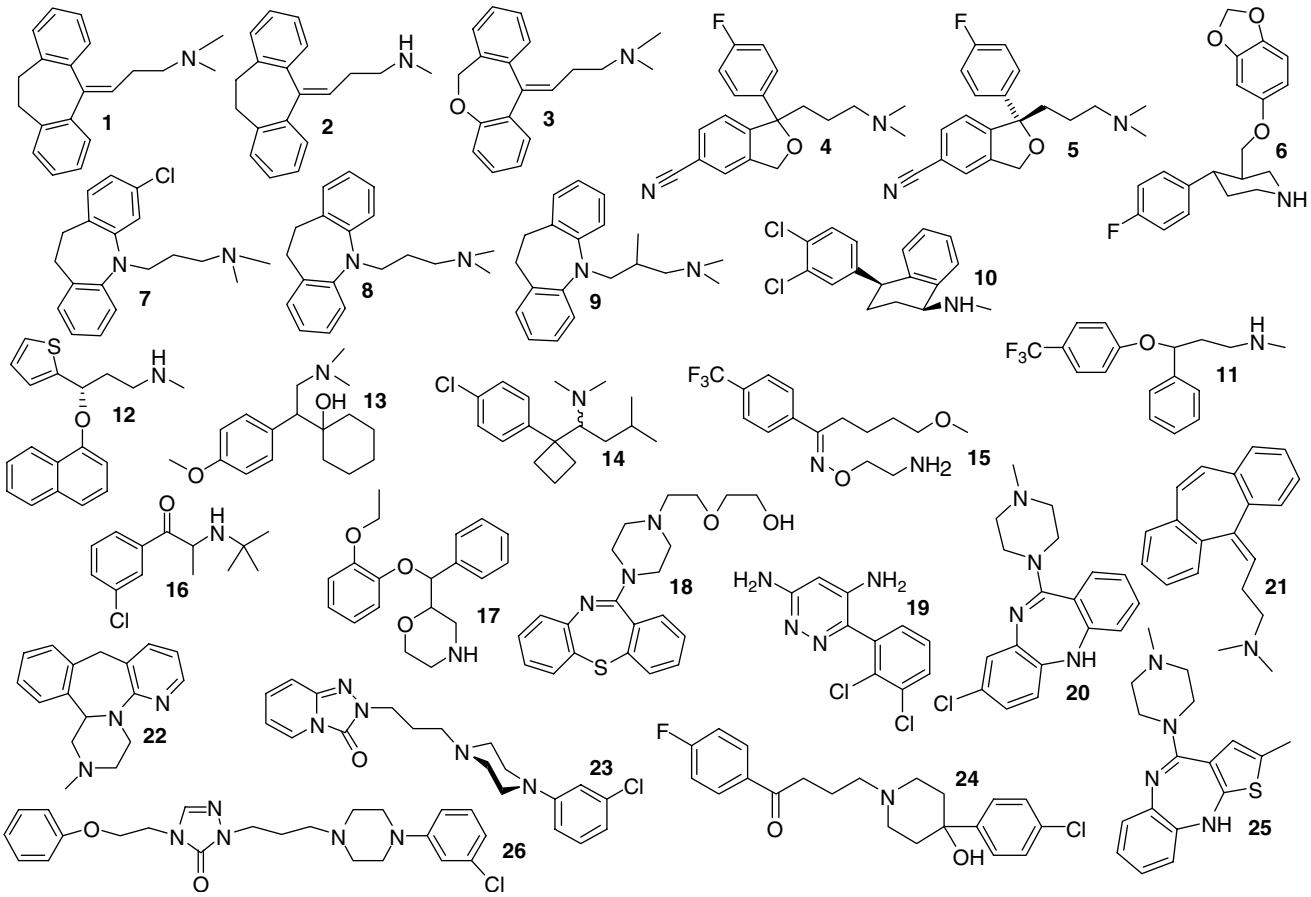

Figure 1. Chemical structures of the detected AD: 1 amitriptyline (TCA), 2 nortriptyline (TCA), 3 doxepine (TCA), 4 citalopram (SSRI), 5 escitalopram (SSRI), 6 paroxetine (SSRI), 7 clomipramine (TCA), 8 imipramine (TCA), 9 trimipramin (TCA), 10 sertraline (SSRI), 11 fluoxetine (SSRI), 12 duloxetine (SSNRI), 13 venlafaxine (SSNRI), 14 sibutramine (SSNRI), 15 fluvoxamine (SSRI), 16 bupropion (NDRI), 17 reboxetine (SNRI), 18 quetiapine (antipsychotic), 19 lamotrigine (antiepileptic), 20 clozapine (antipsychotic), 21 cyclobenzaprine (TCA), 22 mirtazapine (NaSSA), 23 trazodone (SARI), 24 haloperidol (antipsychotic), 25 olanzapine (antipsychotic), 26 nefazodone (DSA).

Table 2. Prevalence of ADs in elite sports in the past decade

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
AD users	8	12	16	8	18	21	21	25	56	73
No. of different AD	3	3	4	4	7	9	10	12	16	17
No. of diff. Sports	5	4	4	3	9	8	10	13	18	22
Total no. of samples	7610	6519	7321	6923	6716	7197	7871	9520	11 685	11 518
Percentage AD/total no.	0.11	0.18	0.22	0.12	0.27	0.29	0.27	0.26	0.48	0.63

Table 3. Numerical distribution of AD users in seven major sport classes

Category	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	AD 1999–2008	Total samples 1999–2008	Percentage 1999–2008
Athletics	1			1	2		1	3		17	25	8800	0.28
Disability sports							1	1	1		3	357	0.84
Endurance	3	9	14	3	9	9	8	4	23	16	98	16 458	0.60
Fighting								1	2	3	6	4832	0.12
Miscellaneous	3	2		1	1	3	1	4	9	15	39	9803	0.40
Power and strength			1		1	5	2	4	7	7	27	8844	0.31
Team sports	1	1	1	3	5	4	8	8	14	15	60	33 786	0.18

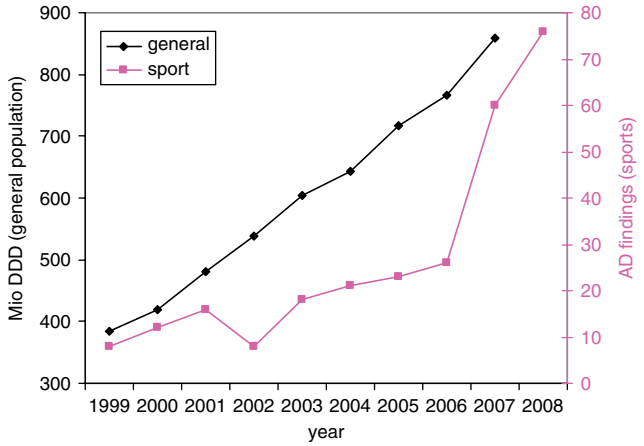

Figure 2. Number of AD findings per year in elite sports from 1999 to 2008 compared to the medicinal prescriptions for ADs in defined daily doses (DDD) in Germany from 1999 to 2007.

distribution of AD classes used in the normal population from 2000–2006. The main AD groups taken by athletes and the normal population were SSRIs and TCAs. The SSRIs constituted 67.8% of all antidepressants used by the athletes, which was more than twice the amount used by the general public (30.7%). The preference of SSRI by athletes might be attributable to better compatibility with elite sport and a side-effect profile that is more acceptable for athletes (minor sedative effects). The SSRIs are frequently mentioned in the media and are promoted as potentially ergogenic aids. This may also explain the popularity of antidepressants in sports. In the general population the lower SSRI percentage was counterbalanced by an increased TCA use. Antidepressants belonging to TCA group were the most often prescribed ADs for the average citizen.

The annual percentage changes in TCA and SSRI consumption were different in the two populations (Figure 4). In Germany, SSRI prescriptions have been growing constantly from 1999 to 2007, whereas the percentage changes in SSRI use in the athletes' group were positive and negative in this period. The relative variations of these analytical findings in the different AD groups are based on very few cases in doping control samples and might therefore reflect a picture with an unpredictable bias.

Over the last ten years samples from 56 643 male athletes, 17 193 female athletes and 9044 samples from athletes with unspecified gender were analysed. From these samples 0.31% males (173 counts), 0.37% females (63 counts) and 0.24% (22 counts) unknowns were tested and confirmed for the presence of ADs. The gender distribution of AD users in the general public has been characterized by a 66 : 34 ratio in favour of the female population. In 2008 only 43 of 74 athletes declared the use of AD medication on the doping control form.

Conclusions

The present study has shown that the use of ADs is evident in the population of top-level athletes. In contrast to the steady increase in AD prescriptions in Germany, the use of AD in sports increased only modestly during 1999–2006 and then more rapidly

Table 4. AD drugs in elite sports in the past decade

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	Number of occurrences from 1999–2008
Amitriptyline	2	2	1		2		4	2	3	5	21
Bupropion									1	2	3
Citalopram	1	1	2		2	7	3	3	9	15	43
Clomipramine				1					1	1	3
Clozapine						1	1		1		3
Cyclobenzaprine								1	1		2
Doxepine						1	1		1	1	4
Duloxetine										1	1
Escitalopram								1	1	3	5
Fluoxetine	5	9	11	4	6	4	3	7	16	10	75
Fluvoxamine								1			1
Haloperidol									2		2
Imipramine										3	3
Lamotrigine							1	2	7	16	26
Mirtazapine				1	1	1			1	3	7
Nefazodone						1					1
Nortriptyline							2		1		3
Olanzapine										1	1
Paroxetine			2	2	4	2	4	3	6	1	24
Quetiapine										1	1
Reboxetine								1			1
Sertraline					1	1	3	1		2	8
Sibutramine									1		1
Trazodone								1			1
Trimipramine										2	2
Venlafaxine					2	3	1	3	8	9	26

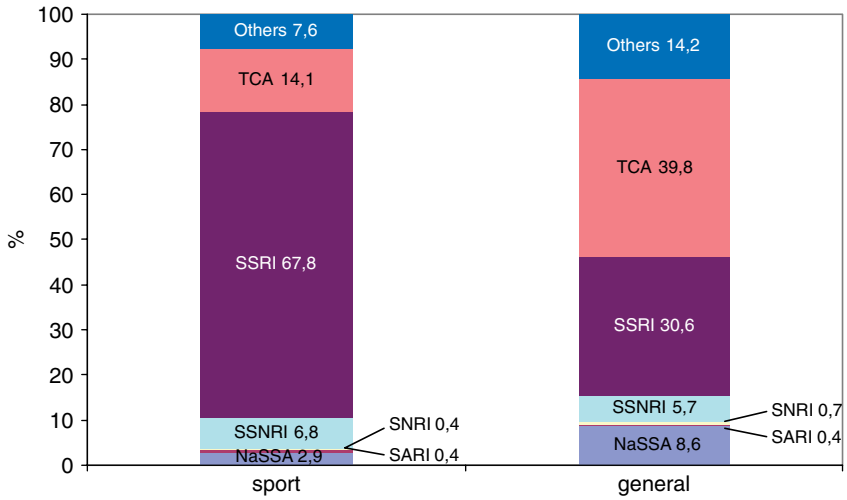

Figure 3. Mean percentage distribution of AD findings in elite sport (1999–2008) and in the general German population (2000–2006) assigned to the designated classes. NaSSA noradrenergic and specific serotonergic antidepressants, SARI serotonin antagonist and reuptake inhibitors, SNRI selective noradrenalin reuptake inhibitor, SSNRI selective serotonin and noradrenalin reuptake inhibitor, SSRI selective serotonin reuptake inhibitor, TCA tri-cyclic antidepressant.

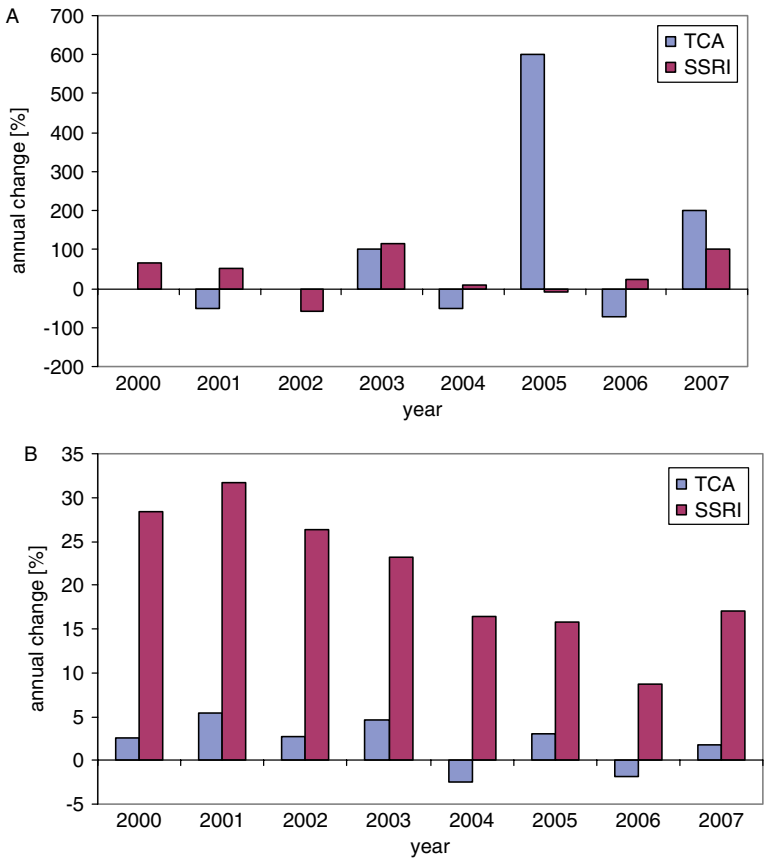

Figure 4. A: Annual percentage changes in TCA and SSRI usage among athletes. B: Annual percentage changes in TCA and SSRI prescriptions in Germany.

in 2007–2008. The variety of different sports concerned with AD and also the variety of different AD drugs have continuously increased over the past decade. In that period endurance athletes were more susceptible to depressive disorders than athletes in other sports and females more than males. The most commonly used class of ADs in sport has been the SSRIs. As the population of athletes is different from the general population (for example in age) its AD consumption should not reflect the consumption behaviour of the general population.

Professional sportsmen are in the public domain and face public criticism. High expectations of their performance and the ubiquitous media presence place athletes under mental pressure, so competitions can become stressful events. Although direct exercise-enhancing effects have not been scientifically proven,[24]

ADs have been promoted and advertised by the media as lifestyle drugs and have achieved a reputation as personality and mood enhancers. According to these myths, the pharmacodynamics of ADs can have an indirect positive influence in training and competition. In a study of the molecular mechanisms of citalopram and cocaine interactions with neurotransmitter transporters[25] the authors described how citalopram and cocaine interacted with the same binding site of the neural serotonin transporter and thus can cause similar ergogenic effects. In contrast to the effects of cocaine, antidepressant drugs have no immediate effect on mood in healthy volunteers or depressed patients;[26] they achieve their effects in the long term after regular administration. In this instance the use of ADs by healthy athletes might compensate for a negative mind-body connection.

Phase II metabolites were not detected by the method used and thus the overall number of AD discoveries in the athletes' group may underestimate the actual number.

A monitoring program for ADs, including all classes of AD, would allow a peer review of the prevalence of ADs in sports on an international basis and their potential for causing significant adverse effects.

The data of the normal population are based on the National Statutory Health Insurance Pharmacy Index,[17] which is limited in some aspects. It does not provide critical information about the effective number of patients in Germany, the duration or dosage of the AD medication trials, the specific condition for which the medication is prescribed or treatment response. Despite these limitations, the National Statutory Health Insurance Pharmacy Index provides a source of representative data concerning the current prescribing practices of ADs in Germany.

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