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Antidepressants in Sport – Therapeutic Use or Doping Abuse?

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Abstract

Since amineptine has been eradicated from the list of controlled substances in 2003 the use of antidepressants by athletes is not restricted by the World Anti Doping Agency (WADA), although some effects might have a positive influence on the athlete's performance.

The introduction of the new selective serotonin reuptake inhibitors (SSRI) in the past decade has led to an increasing number of antidepressant occurrences, which have routinely been detected by the screening procedure for stimulants (Scr. I). This has induced us to monitor the developments over the past four years. Statistical distributions according to the total number of prescriptions in Germany and according to different sports and gender are reviewed and discussed.

Scr. I procedure allows for recording of analytical data e.g. relative retention times and mass spectra of the most abundant antidepressants and metabolites, which are also presented in this paper.

Introduction

The therapeutic use of prescriptional antidepressants is confined to the following indications:

1. Major depressive disorder, 2. dysthymic disorder, 3. bipolar disorder.

Certain agents have also shown usefulness in the treatment of other disorders (table 1).

All these mental disorders result from a complex and multifactorial disharmony in social and chemical structures. The most accepted view is that depressions arise from an imbalance of neurotransmitter amines (e.g. noradrenaline, serotonin) in the brain [1,2].

Main Indications:
Major Depressive Disorder
Dysthymic Disorder
Bipolar Disorder
New Indications for Certain Antidepressants:
Generalized Anxiety Disorder (Venlafaxine)
Panic Disorder (Sertaline, Paroxetine)
Posttraumatic Stress Disorder (Sertraline)
Social Phobia (Paroxetine)
Bulimia Nervosa (Fluoxetine)
Obsessive-Compulsive Disorder (Fluvoxamine, Paroxetine, Sertraline, Fluoxetine)
FDA approved Fluoxetine (Prozac®) for:
Obesity, Smoking Cessation, Alcoholism
Borderline Personality Disorder
Premenstrual Dysphoric Disorder
Geriatric Depression

Table 1: Indications for the therapeutic use of antidepressants.

According to the site of action modern antidepressants can be devided into 5 classes (table 2).

	Class	Substances
SSRI	Selective Serotonin Reuptake Inhibitors	Citalopram, Escilatopram, Fluoxetin, Fluvoxamin, Paroxetin, Sertralin
SNRI	Selective Noradrenaline Reuptake Inhibitors	Reboxetin
SSNRI	Selective Serotonin and Noradrenaline Reuptake Inhibitors	Venlafaxin, Duloxetin, Sibutramin
NaSSA	Noradrenaline and Serotonin Specific Antidepressants (α_2-Antagonists)	Mirtazapin
RIMA	Reversible Inhibitors of Monoaminoxidase-A	Moclobemid

Table 2: Classification of modern antidepressants.

Figure 1 shows schematically the synaptic signal transduction between two neurons:
A primary signal induces the secretion of neurotransmitters, e.g. serotonin and noradrenaline into the synaptic gap. The transmitters bind at specific protein G associated receptors, which effect the formation of second messengers and transcription factors. The signal cascade results finally in the biosynthesis of specific proteins, so-called brain derived neurotrophic factors (bdnfs). A lack of these bdnfs is believed to contribute to the development of mental illness [1,2]. Most antidepressants interfere with this mechanism in that they increase the concentration of neurotransmitter in the synaptic gap.

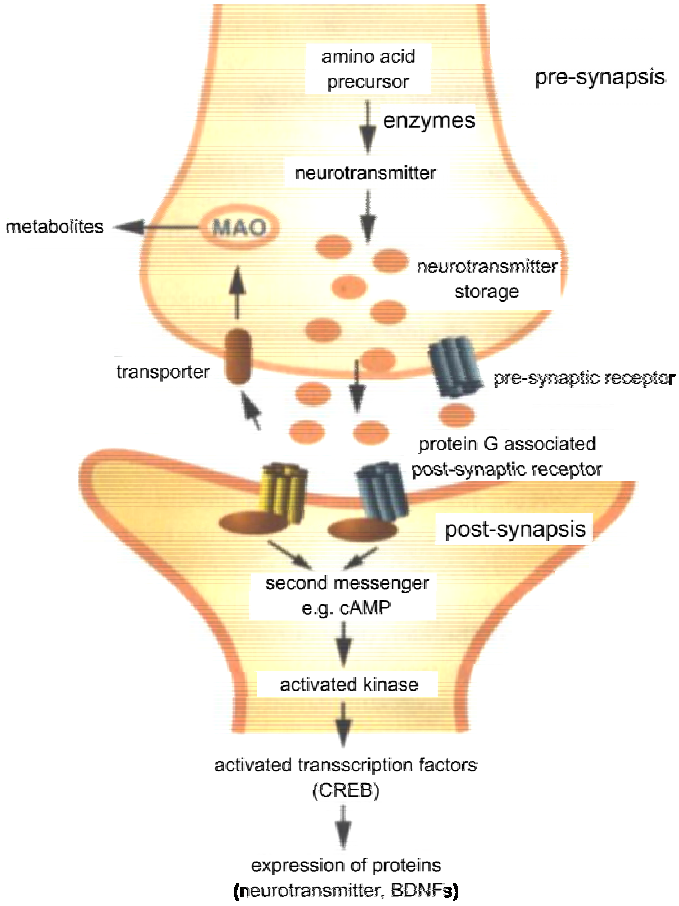

Figure 1: Schematic signal transduction between two neurons in the brain.

Increasing importance has been gaining the class of selective serotonin reuptake inhibitors (SSRI). They are chemically and pharmacologically distinct from the classical tricyclic antidepressants like imipramin and amitriptyline. SSRI combine an aromatic ring with an amino group and consist of at least two stereo isomeric forms (figure 2).

The pharmacology of SSRI can be explained by a blockade of the serotonin transporter protein (sert), which provide the back transport of serotonin into the presynaptic neuron. As a consequence the retention time of serotonin between two neurons is prolonged and the signal intensified. In contrast to all the conventional tricyclic antidepressants the new generation of antidepressants does not bind to unspecific central receptors, which gives them a much more acceptable side-effect profile. This may be one of the reasons for their fast growing market. The total number of prescriptions of SSRI in Germany has more than decupled over the last ten years [3].

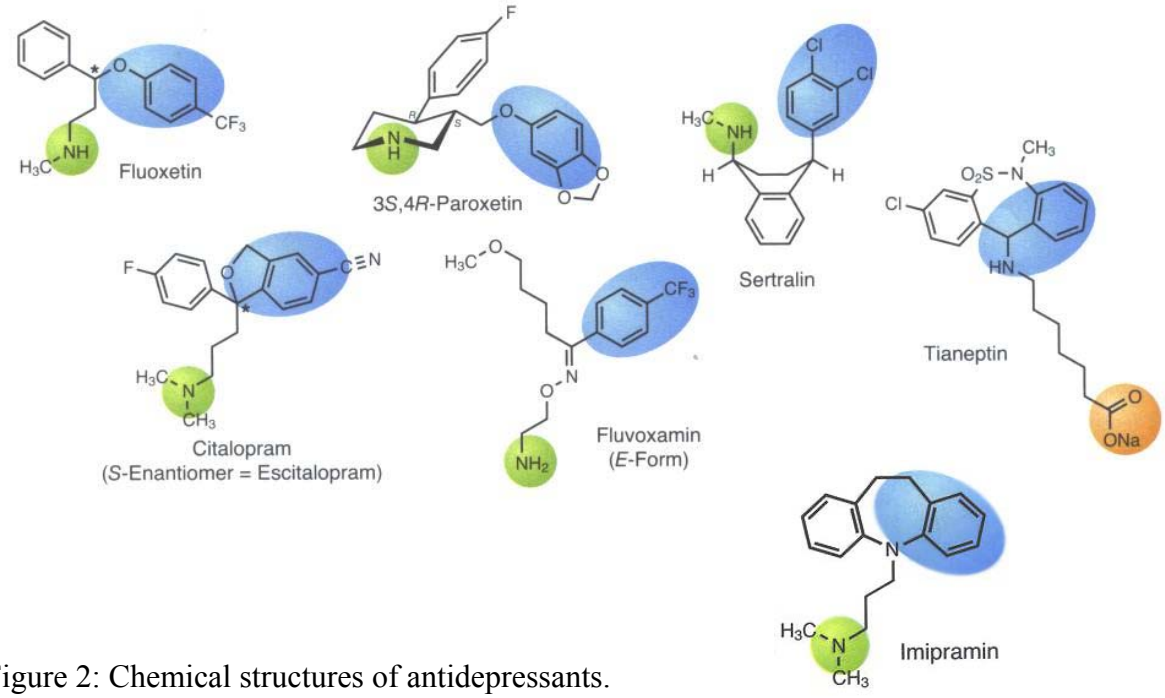

Figure 2: Chemical structures of antidepressants.

Experimental

All samples have undergone the routine screening procedure for stimulants. The sample preparation and analysis of stimulants in doping control is described elsewhere [4].

Results

Electron ionisation mass spectra (EI-MS) of a selection of antidepressants, that have been detected in our lab within the last 4 years are shown in figure 3. Fluoxetin (Prozac®), venlafaxin and citalopram can be characterized by their molecular ions and a fragment m/z 44 or 58, which are formed by α–cleavage.

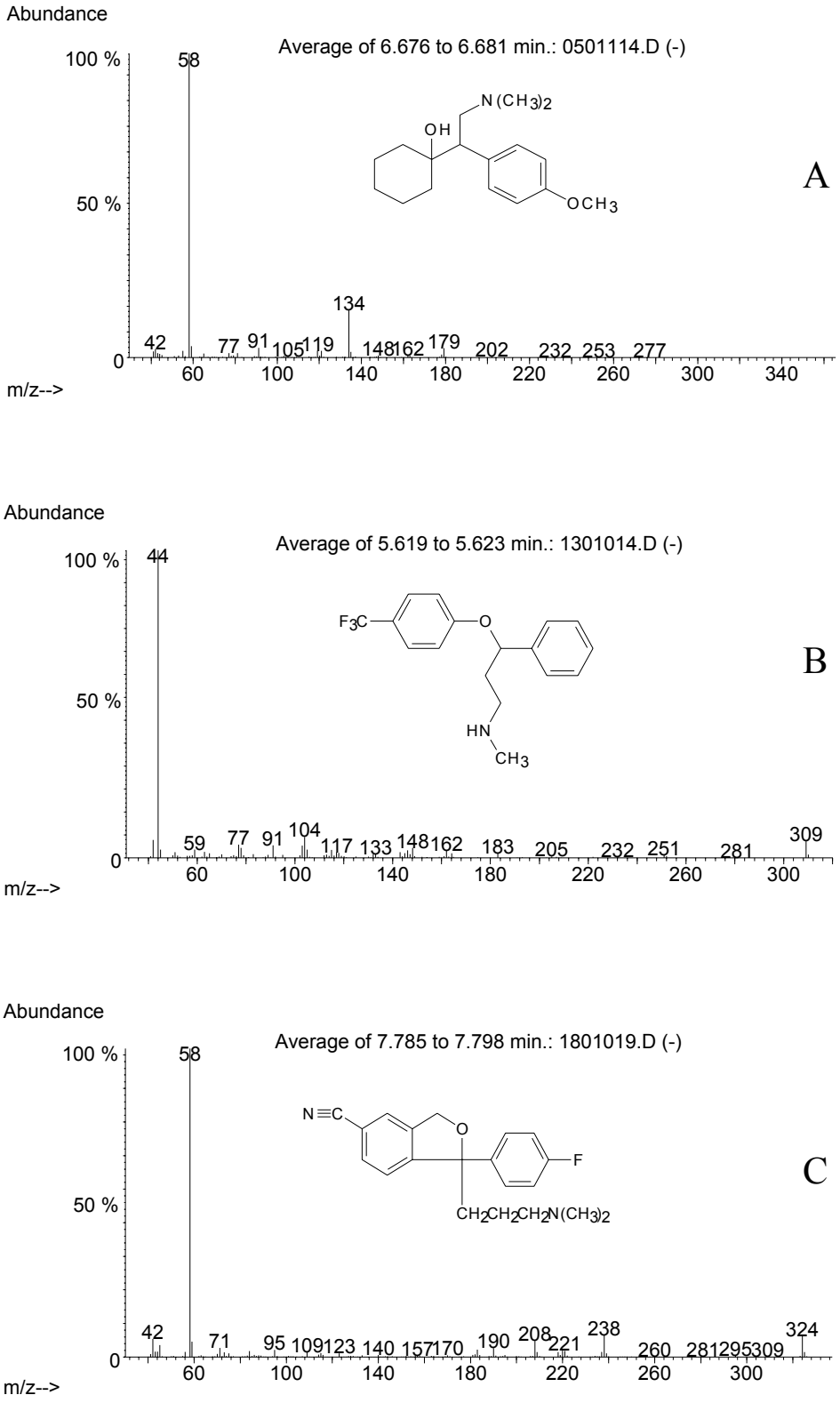

Figure 3: Molecular structures and electron ionisation mass spectra of venlafaxin M^+ 277 (A), fluoxetin M^+ 309 (B) and citalopram M^+ 324 (C).

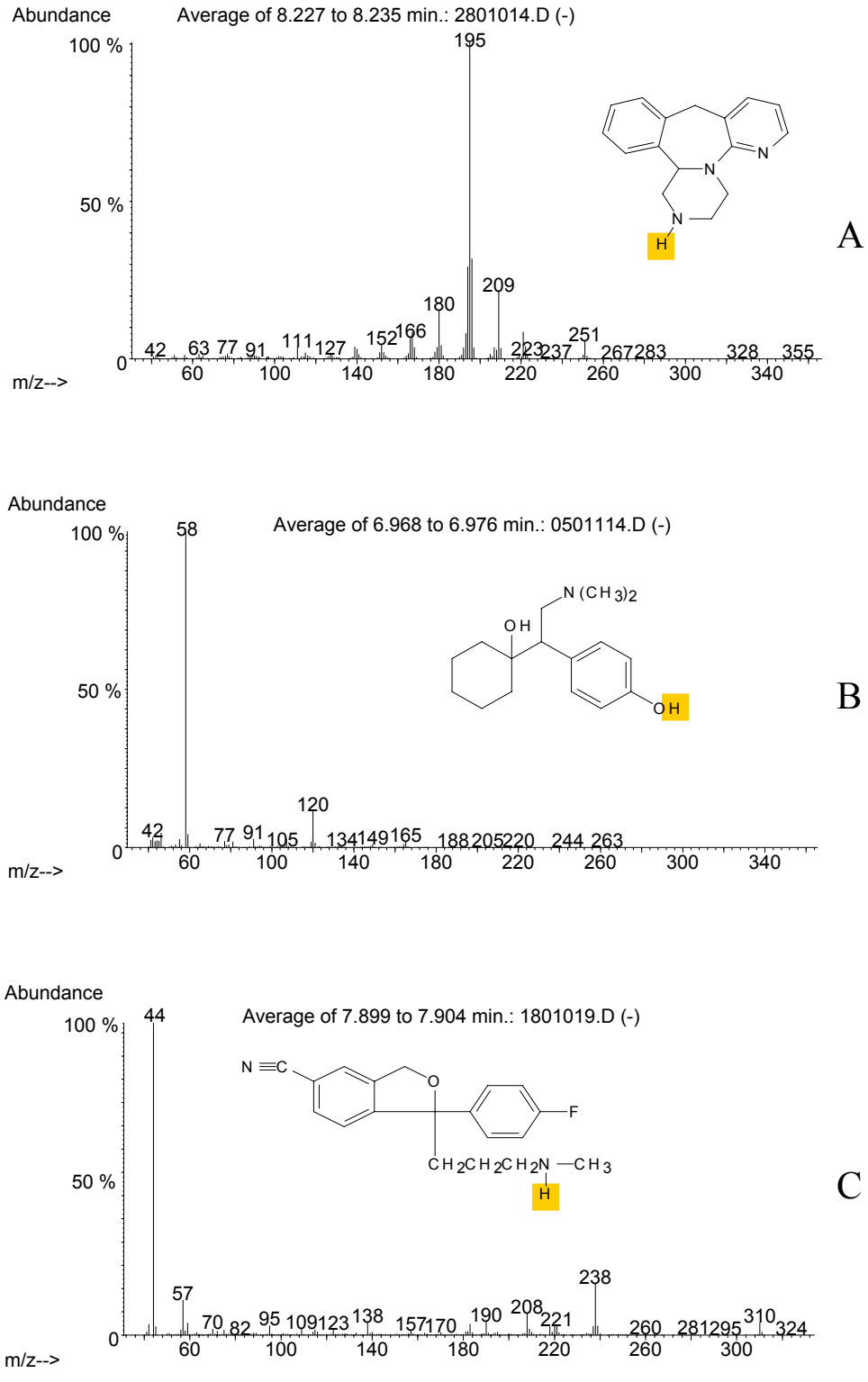

Figure 4: Molecular structures and electron ionisation mass spectra of N-desmethyl-mirtazapin M^+ 251 (A), O-desmethyl-venlafaxin M^+ 263 (B) and N-desmethyl-citalopram M^+ 310 (C).

We were also able to identify N- and O-demethylated metabolites (figure 4), which are in agreement with reports from the literature [5]. Other pathways include hydroxylation and conjugation, which are not covered by scr I procedure. Nevertheless most antidepressants are excreted at least partially free in urine and can be isolated by basic liquid-liquid extraction without hydrolysis. The analytical data revealed a significant number of antidepressant users and an increasing diversity of used substances (tables 3 & 4). Table 3 lists the antidepressant users according to their sports and table 4 contains the different antidepressive substances that have been found in the last 4 years. The use of antidepressants seems to be a sport specific problem, e.g. cyclists are more susceptible to depressive disorders than other athletes. Analysis of the gender distribution of antidepressant users within the athlete‘s group revealed a predominance of male users (data not shown).

	2001		2002		2003		2004		2005 (Jan-Feb)	
	Antidepr.	Total	Antidepr.	Total	Antidepr.	Total	Antidepr.	Total	Antidepr.	Total
Endurance	12	840	5	533	7	404	9	562	2	102
Power&strength	1	382	-		3	343	4	635	1	12
Team sports	1	93	3	1827	5	1558	4	2588	2	254
Miscellaneous	2	157	1	16	3	93	2	95	-	
Total Antidepr.	16		9		18		19		5	

Table 3: Numerical distribution of antidepressant users in different sports.

2001	2002	2003	2004	2005 (Jan-Feb)
Fluoxetin	Fluoxetin	Fluoxetin	Fluoxetin	Fluoxetin
Paroxetin	Paroxetin	Paroxetin	Paroxetin	Paroxetin
Citalopram	Mirtazapin	Sertralin	Sertralin	Sertralin
Amitriptylline	Clomipramin	Citalopram	Citalopram	
		Venlafaxin	Venlafaxin	
		Mirtazapin	Mirtazapin	
		Amitriptylline	Doxepin	

Table 4: Antidepressants detected in the last 4 years.

Conclusions

Our preliminary data have shown that the use of antidepressants is evident in the population of athletes. The consumption of antidepressants by athletes does not correlate to that of the normal population: 1. Predominance of cyclist users, 2. preference of SSRI,
3. gender statistics in the athlete's group does not reflect the distribution of the normal population, where females are more affected by depression than males. Although direct exercise enhancing effects have not been proven [6], the pharmacodynamics of antidepressants might exhibit effects, which have an indirect positive influence in training and competition (table 4). Under these circumstances antidepressants used by actually healthy athletes would become a doping relevant issue. On the other hand the effects in table 4 have only been perceived by people with mental illness. If similar pharmacodynamic effects are being experienced by healthy people is still unknown. However, most recently the SSNRI (Selective Serotonin and Noradrenaline Reuptake Inhibitor) sibutramin is being proposed to be added to the group of stimulants on the new WADA list of 2006.

- Stimulating or Relaxing Effects (depending on the Antidepressant)
- Improved Cognitive and Coordinative Faculties
- Improved Motivation
- Euphoric/Optimistic Mentality
- Enhanced Self-Confidence
- Anxiolytic Effects
- Antiemetic Effects

Table 4: Potential doping relevant effects of antidepressants.

Acknowledgements

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References

[1] Duman, R.S. (2004) Role of neutrotrophic factors in the etiology and treatment of mood disorders. Neuromolecular Med. 5 (1), 11 – 26.

[2] Schildkraut, J.J. (1965) The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am. J. Psychiatry 122, 509 - 522.

[3] Lohse, M.J.; Lorenzen, A. and Müller-Oerlinghausen, B. (2004) Kapitel 43. Psychopharmaka. In: Schwabe, U. and Paffrath, D. (Eds.), Arzneiverordnungsreport 20. Ausgabe, Springer-Verlag, Berlin, 769 - 810.

[4] Donike, M.; Geyer, H.; Gotzmann, A.; Kraft, M.; Mandel, F.; Nolteernsting, E.; Opfermann, G.; Sigmund, G.; Schänzer, W. and Zimmermann, J. (1987) Dope analysis. In: Belloni, P.; Benzie, G. and Ljungquist, A. (Eds.), Official Proceedings: International Athletics Foundation World Symposium on Doping in Sport, Centro Studi & Ricerche, Firenze, 53 - 80.

[5] Härtter, S. (2004) Moderne Antidepressiva: Pharmakokinetik, Interaktionspotential und TDM. Pharmazie in unserer Zeit 4, 296 - 303.

[6] Meeusen, R.; Piacentini M.F.; Van Den Eynde, S.; Magnus L. and De Meirleir, K. (2001) Exercise performance is not influenced by a 5-HT reuptake inhibitor. Int. J. Sports Medicine 22 (5), 329 – 336.