ALL MEDICINES ARE DRUGS BUT NOT ALL DRUGS ARE MEDICINES: PHARMACOEPIDEMIOLOGICAL APPROACHES TO ASSESS THE USE OF PRESCRIPTION/OTC MEDICINES, HERBS, DIETARY SUPPLEMENTS AND ILLICIT DRUGS

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Introduction

My PhD study programme has been focused on pharmacoepidemiologic topics.

Pharmacoepidemiology applies epidemiologic reasoning, methods and knowledge to the study of the uses and effects, beneficial and harmful, of medications in a defined population.

Pharmacoutilization studies, in particular, aim at collecting the prescriptive profile of the sample investigated.

Beside risk/effectiveness evaluations or the compliance assessment to a treatment, drug intake may be a indirect clue of the healthiness of the studied population since it is the marker of a disease severe enough to require a medication.

Data concerning the use of prescribed medications and over the counter (OTC) may also allow to evaluate potential risks of drug-drug interactions (DDI) which represents a particular concern especially in the elderly, where polypharmacy is extremely common.

DDI may be represented by a pharmacokinetic or pharmacodynamic interference of drugs on each other, which can determine an impaired effectiveness or an increased toxicity and is one of the main causes of adverse drug reaction, being responsible for up to 23% of hospital admissions (Secoli 2010).

In this context I have performed a pharmacoutilization study investigating the risk of potential DDI between treatment potentially used in dentistry and the prescribed medications/OTC used by outpatients attending a dental clinic.

Moreover, pharmacoepidemiology surveys offer the possibility to investigate use and attitudes towards other agents such as dietary supplements (DS), herbal remedies (HR) and illicit substances such as doping.

Indeed, the use of the these substances appears to be raising, thought studies in literature are quite scarce.

Therefore, I decided to investigate the use, knowledge (benefits and risks) and attitudes towards these agents within sports.

I have also deepened the herbal remedies topic HR performing an extensive review of the existing literature and followinf s muticenter study in the setting of multiple sclerosis.

Prescribed medication and risk of DDI in dentistry

Drug profile in patients attending dental clinics has been poorly investigated since the few pharmacoutilization studies present in literature were often focused on the use of drugs by the dental practitioner (Gómez-Oliván 2007; Ciancio 1998) and, in some cases, on specific class of medications such as NSAID or antimicrobials (Epstein 2000; Cherry 2012; Levrini 2008).

Therefore, though the most common medication prescribed in dentistry presents a large therapeutic index, DDI with prescribed medication, as well as with DS or HR may occur (Moore 1999-partI). Indeed, since they do not require prescription, DS and HR become in the last decades a substantial and growing part of health-care behaviour in affluent nations (Bailey 2012).

The risk of DDI in dental patients is a matter of concern since the prevalence of elderly dental patients is growing and the need for complex procedures is raising (Hersh 2008). Polypharmacy and pharmacokinetics/pharmacodynamics changing due to aging make these subjects especially vulnerable to risk for adverse drug reactions and DDI (Corsonello 2010).

The aim of the following study "Prescribed medication and risk of drug-drug interaction in dentistry: a survey in ambulatory patients" was to investigate the risk of DDI in dentistry patients investigating any potential interaction between drug or DS/HR used and common treatments in dentistry.

Prescribed medication and risk of drug-drug interaction in dentistry: a survey in ambulatory patients

Abstract

Objectives: Drugs used in dental practice have often a large therapeutic index, are usually in a single dose or in short-term form and frequently used for elective procedures, however, drug-drug interactions (DDI) with prescribed medication, as well as with dietary supplements (DS) or herbal remedies (HR) may occur. Nevertheless, pharmacoepidemiologic data in this field are scarce. The aim of the present study was to investigate the risk of DDI in dentistry patients investigating use pattern of drugs and DS/HR.

Methods: Dentistry outpatients were consecutively enrolled and surveyed through a semi-structured questionnaires divided into three sections in order to collect sociodemographical, pharmacological, DS and HR data. Potential risk of interactions was evaluated checking any potential interaction reported in literature between the drugs, DS and HR used in the studied population and treatments commonly used in dentistry practice.

Results: 100 patients were enrolled, 37% were under prescribed medications, mainly represented by cardiovascular drugs. 82 potential DDI were detected and were principally represented by potential interactions with NSAIDs (88%) and antimicrobials (75%).

Conclusions: The study underlines that dentistry outpatients are often under a pharmacological tretament and polypharmacy is not unfrequent, with a high risk of DDI with treatment prescribed by the dentist. Therefore, a careful evaluation of all the medications including DS and HR and a the knowledge of potential interactions with dentistry treatments is mandatory to avoid the risk of DDI.

Introduction

Little is known about drug prescription and use in patients attending dental clinics (Carter 2007; Brindley 2003; Miller 1992). Indeed, the few studies present in literature available are often focused on drug prescription by the dental practitioner (Gómez-Oliván 2007; Ciancio 1998) and, in some cases, on patient use of specific class of medications such as NSAID or antimicrobials (Epstein 2000; Cherry 2012; Levrini 2008).

The most common medication prescribed in dentistry are represented by a limited number of therapeutical agents: antimicrobials, analgesics, local anesthetics, sedatives and axiolytics and vasoconstrictors (Gómez-Oliván 2007; Ciancio 1998). Though these medication have often a large therapeutic index, are usually in a single dose or in short-term form (five to 10 days) and frequently used for elective procedures, drug-drug interactions (DDI) with prescribed medication, as well as with dietary supplements (DS) or herbal remedies (HR) may occur (Moore 1999).

DDI can be defined as a pharmacokinetic or pharmacodyamic interference of drugs on each other, which may result in impaired effectiveness and/or increased toxicity. Indeed, DDI is one of the main causes of adverse drug reaction, being responsible for up to 23% of hospital admissions (Secoli 2010).

Since drug use increases significantly with age (Moore 1999-partI) the polypharmacy is common among older people, representing a major concern in the care of these subjects. In addition aging is associated changes in pharmacokinetics such as impaired drug clearance and pharmacodynamics with a progressive decline in homeostatic mechanisms, make these subjects especially vulnerable to risk for adverse drug reactions and DDI (Corsonello 2010). Moreover, the prevalence of elderly dental patients is growing and due to the reduction of edentulism and tooth loss, the need for complex periodontal, implant and restorative procedures is raising (Hersh 2008).

Similarly to elderly patients, paediatric dental patients due to their particular physiology and anatomy (increased receptor sensitivity, narrow nares, large tongue, high glottis, smaller diameter of the airway passages) are particularly vulnerable to drug interactions, especially involving multiple central nervous system agents such as local anaesthetics together with narcotic sedatives (Hersh 2008).

Besides prescription medicines, another source of DDI is increasingly represented by dietary supplements (DS) or herbal remedies (HR). DS and HR do not require prescription and they became in the last decades a substantial and growing part of health-care behaviour in affluent nations (Bailey 2012).

Therefore, the aim of the present study was to investigate the potential for DDI in dentistry patients by assessing in a cohort of outpatients attending a dental clinic: (i) the use pattern of prescription and non-prescription medicines as well as of DS/HR; (ii) the relationship between medicines and/or DS/HR use and socio-demographic features of the surveyed population; (iii) the potential for the occurrence of DDI between medicines and/or DS/HR used and common treatments in dentistry.

Materials and methods

The Department of Orthodontics is a University Clinic (University of Insubria, Varese, Italy) where a mean of 180 specialist visits takes place each month. Two kinds of typical patient may be observed: the first one is represented by under 15 who are part of prevention programs of odonthoiatric pathologies or require orthodontic treatments. A second group of patients is composed by adults with complex odonthoiatric conditions.

Patients who attended the Department of Orthodontics for a specialist visit and giving their written consensus to participate to the survey were consecutively enrolled from January to February 2010.

Participants were surveyed through a semi-structured questionnaire devised to investigate: socio-demographical characteristics: age, sex, body mass index (BMI), education, place of living; pharmacological treatment: drug used, dose regimen, root of administration; use of DS/HR (name, composition, dose regimen, route of administration).

All the information were gathered through a telephonic interview when the patients were at home and had the time to check for the proper name of drug as well as DS/HR used.

The study was conducted in accordance with the WMA Declaration of Helsinki and written informed consent was obtained from all participants.

To investigate the potential risk of interactions, the drugs as well as DS/HR used were examined singularly with the aim to check any potential interaction reported in literature with treatments commonly used in dentistry practice.

Data analysis

Collected data were inserted in a digital archive and analyzed through a descriptive approach. Data were expressed as mean±standard deviation (SD). Anthropometric data, height and weight were expressed as body mass index (BMI, kg/m^2). Prescribed drugs were codified according to the WHO Anatomical Therapeutic Chemical (ATC) classification system (http://www.whocc.no/atc/structure_and_principles/). Statistical significance of the differences among groups was examined using the χ^2-test distribution, the unpaired t-test, ANOVA or the Pearson correlation test, as appropriate.

Results

Socio-demographic features

100 subjects (56% male) with a mean age of 33.3±25.6 years (range 2-87) were consecutively enrolled. In 41% of cases patients were younger than 15 years. Even if excluded the youngest groups (i.e., <15 years and 15 to 24 years), a primary level of education was reported in the majority of cases (24%). Table 1 shows the socio-demographic features of the whole sample, as well as divided according to age group.

Drug use

37% of the population (59% male, mean age 52.5±23.9 years) were under a pharmacological treatment, for a total of 103 medication, 2.8±2.0 per user (range: 1-8). In table 2 the use of medications among the different classes of age is described in details. Cardiovascular drugs were the most commonly used medications (33%) and were used by 54.1% of patients (Table 4). If considered the singular active principle, the mainly represented was acetylsalicylic acid (8.7%), used as antithrombotic preparation by 24.3% of the patients.

Dietary supplements/Herbal remedies

6%, 5 female and 1 male, with a mean age of 34.5±13.7 years (range: 19-56) used on the whole 7 DS/HR, a mean of 1.2±0.4 DS/HR per subject (range: 1-2). The substances were represented by a complex of aminoacids together with vitamins B group in 5 cases (71.4%), and by HR in the remaining 2 (Undaria pinnatifida associated with Opundia Ficus-indica in one case, and Lagerstroemia, Ginseng, Blueberry, royal jelly and Eleutherococcus in the other case).

Potential drug-drug interaction

82 potential interaction with medication commonly used in dentistry were observed in 24 subjects (64.9% of patients under medication), with a mean of 3.4±2.5 DDI/subject (range: 1-8) In Table 5 are presented all the potential DDI with drugs commonly used in dentistry.

The contemporary intake of medications and DS/HR occurred in only one subjects (carbocisteine together with an aminoacid supplement). However, no literature data concerning potential risk of interaction with the medication used were found.

Correlations

Drug use presents a linear correlation with age (r^2=0.29; *P*<0.0001). Potential DDI were related to the number of drugs used (r^2=0.65; *P*<0.0001). None of the other socio-demographic features considered appeared to be relate to the pattern of drug use.

The intake of DS and HR were neither influenced by socio-demographic features nor by drug use.

Number of medication used as well as age, significantly differed between the subjects at risk for DDI and who were not (3.6±2.0 *vs* 1.2±0.5 drug/subject, respectively, *P*<0.0001; 64.3±14.1 *vs* 31.2±24.1 years, respectively, *P*<0.0001). Linear correlations were observed between age (r^2=0.17; *P*<0.01) and number of drug used (r^2=0.59; *P*<0.0001).

Discussion

Medication, DS and HR use

The use of prescribed medications interested one third of the studied population and was comparable to available data in similar setting (26-44%) (Carter 2007; Brindely 2003; Miller 1992).

As occurs also in the general population, prevalence and number of drugs used increased with age with a linear correlation (Rapporto OSMED 2009; Carter 2007; Miller 1992), reaching a prevalence of 100% in the over 64.

Cardiovascular drugs are the most common drug group that dentists encounters, interesting half the patients as also observed in our sample (Becker 2007; Carter 2007).

In particular, ASA, used as antiplatelet drug, resulted the most prescribed active principle (8%), in accordance with a prevalence of 8% in the general population (Rapporto OSMED 2009).

The prevalence of HR and DS, interesting 6% of the studied population, was similar to that reported in literature the Italian population (Menniti-Ippolito 2002). We are aware that DS and HR are often under reported by the patient during the visit, for that reason a specific section of the questionnaire was devoted to the use of these substances.

DS use appears to be spread interesting up to half of in the general population (Bailey 2012), however, though the intense marketing and promotion, only a few rigorous studies have been performed, therefore, the actual advantage of supplementation is controversial (Dascombe 2010). A balanced diet allows to avoid the risk of vitamin or mineral deficiency, therefore, dietary supplementation is usually unnecessary if not dangerous since DS may cause adverse reactions due to contaminants or other substances (such as drugs) not declared on the label (Gullotti Codaro 2011; Geyer 2008).

Moreover, the use of HR represents a matter of concern especially in particular groups of individuals (such as children, elderly, pregnant women), or in patients suffering from chronic disease and/or undergoing to surgery, who may present physiological or pathological differences in herbal metabolism, a potential increased risk of adverse events or interferences with conventional treatments.

Potential drug-drug interaction

More than 80 potential DDI have been found in two thirds of drug users. The risk for DDI was related to the number of medication used and the group at risk used a mean of more than three drugs (up to 8 drugs). Not surprisingly, due to the direct correlation to the number of drug used, also age presented a linear correlation with DDI risk. Polypharmacy is common in the elderly and is a major concern in the care of these subjects, due polymorbidity, with increased number of chronic diseases and changing in the pharmacokinetic and pharmacodynamic response (Corsonello 2010) and the higher risk of adverse drug reactions and DDI (Planton 2010; Antithierens 2010).

It has been estimated that more than 30% of drugs taken by dental outpatients may produce dentally related side effects, such as xerstomia, abnormal bleeding, etc, but also DDI, and this percentage raises up to 90% in the elderly (Miller 1992).

The exact prevalence of DDI risk in dentistry has so fare not clearly been established. The findings of the present study were used to discuss the potential DDI with drugs commonly prescribed in dentistry in the light of the available literature.

Antimicrobials

Antifungal azolics and antibiotics represented are commonly used in dental practice (Hersh 1999). If excluded single-dose prophylactic regimens for endocarditis and articular prothesis, the treatment with antimicrobial agents is usually more prolonged than other types of drug, from 5 to 10 days (Hersh 2008; Hersh 1999). Therefore, the patient is exposed to a increased risk of DDI, compared to other drug classes, due to the fact that some antimicrobials are able to inhibit gut and liver cytochrome P450 system, enhancing, therefore, plasma levels of other drugs that share the same metabolic pathway and increasing the toxicity (Hersh 1999) .

Indeed, antibiotic (clatithromicin, erythromycin, ciprofloxacin and metronidazole) as well as antifungal azolics (fluconazol, ketoconazol) are potent inhibitors of several cytochrome P(CYP)450 isoforms. In particular CYP1A2 is inhibited by macrolids (erythromycin, clarithromycin) and ciprofloxacin, CYP2C9 is inhibited by metronidazole and antifungal azolics (fluconazol, ketoconazol) and CYP3A4 is inhibited by macrolids (erythromycin, clarithromycin), metronidazole and antifungal azolics (fluconazol, ketoconazol (Hersh 2008; Sims 2007; Gomez-Moreno 2009; Hersh 2004).

We found 27 potential interaction with antimicrobial treatment in 3 quarters of the drug users.

Anticoagulants

The potential severe DDI with antimicrobials are mainly represented by interactions with anticoagulant treatment (warfarin, acenocoumarole) (Hersh 1999), due to the relatively low therapeutic index of these drugs. Patients with prosthetic heart valves are considered at high risk for infective endocarditis and need to be treated with a single oral dose of penicillin and only isolated cases of increased prothrombin time and bleeding have been reported, suggesting the importance to monitor the patients under anticoagulant treatment (Bhatt 2000).

Macrolids, metronidazole and fluconazole may be involved in the interaction with oral anticoagulants such as warfarin (metabolized by CYP2C9 and CYP3A4) and acenocoumarole (metabolized by CYP2C9) increasing prothrombin time and INR with risk of bleeding (Gomez-Moreno 2009; Horn 2010; Howard-Thompson 2008; Thijssen 2003). In addition, also topical use of antifungal oral gel may be a poorly recognize way of interfere similarly anticoagulant activity (Silingardi 2000; Ezsias 1997).

Antibiotic treatment with tetracyclines or other broad spectrum antibiotics may alter gut flora and impair the absorption of vitamin K, essential cofactor in the synthesis of vitamin K-dependent clotting factors VII, IX, X (Sims 2007). However, significant interactions may

occur only in patients with poor vitamin K intake (Hersh 1999). Several cases of increased INR and bleeding in patients under oral anticoagulants prescribed also tetracycline have been reported in literature (Stockley 1996; Westfall 1980; O'Donnel 1989), though one study observed no interactions (Hersh 1999).

Moreover, cases of increased anticoagulant activity under amoxicillin and ampicillin and one report about a slight reduction of prothrombin times in five patients taking amoxicilln appeared in literature (Hersh 1999). These evidence suggests that the potential interactions of these last antibiotics is rare and unpredictable and may be of most concern in patients with deficient intake of vitamin K.

Therefore, before prescribing metronidazole, tetracycline or antifungals azoli in patients on chronic anticoagulant treatment a consultation with the prescribing physician is advised.

Azythromicin presents a few interactions with drugs metabolized by CYP3A4 and may be, therefore, a safe alternative in patients treated with drugs metabolized by CYP3A4 (Gomez-Moreno 2009).

Since metronidazole is usually prescribed for anaerobic component of oral infections together with penicillin used for the aerobic one, clindamycine has been suggested as a valid alternative in these cases (Gomez-Moreno 2009)

Proton pump Inhibitors

Ketoconazole absorption could be impaired by the reduction of gastric acidity consequent to proton pump inhibitors use (Hersh 2008; Blume 2006). Therefore, antifungals efficacy should be significantly impaired in the two patients of the study who were under omeprazole or lansoprazole.

Immunosuppressants

DDI with tacrolimus used as immunosuppressant in solid organ transplant as well as in the treatment of autoimmune disorders (psoriasis, rheumatoid arthritis) has been described in literature (Gomez-Moreno 2009). Tacrolimus is a substrate of CYP3A4, therefore, the inhibition of this isoenzymes by macrolids may determine the substrate accumulation and leading, therefore, to an excessive immunodepression and nephrotoxicity (Gomez-Moreno 2009).

Estrogens and progestines

The potential contraceptive failure under antibiotic treatment is controversial (Sims 2007; Hersh 1999). Estrogens and progestines as substrate of CYP3A4 (Hersh 2008; Hersh 2004), but, none of the commonly used antibiotic in dentistry are inhibitors of CYP3A4 and may, therefore, raise the level of oral contraceptive (Back 1990). Though cases of contraceptive failure have been reported in literature (Bainton 1986), clinical studies have not proven significant reduction in blood levels of these drugs neither of their efficacy (Hersh 1999). The anecdotic cases may be due to an impairment in the enterohepatic recycling of the conjugated estrogens reactivated, liberating the parent compound by gut flora and reabsorbed as active drug (Sims 2007; Gomez-Moreno 2009), observed in animal models (Hersh 1999; Gibson 1994; Back 1982). Though the real effects are still debated, dentist should inform oral contraceptive users concerning the potential risk of this DDI.

Statins

Macrolids and azole antifungal agents should be avoided in patients under statins. Increased levels of statins may determine higher risk for myophaty and hepatotoxicity (Becker 2008). Significant cases of rabdomyolisis, due to the association of statins and antimicrobial has been

reported especially for simvastatin due to the fact that, together with atorvastatin, is substrate of CYP3A4 (Mazzu 2000). CYP metabolism of rosuvastatin appears to be minimal and is principally mediated by the 2C9 enzyme, with little involvement of 3A4 (Thijssen 2003).

Calcium-channel blockers

Calcium-channel blocker such as Verapamil may compete with macrolide for CYP3A4. As a consequence, toxicity due to elevated levels of macrolides (cardiac toxicity due to prolonged QT) or verapamil (bradycardias and atrioventricular block) may occurr.

Drugs acting on central nervous system

Lorazepam, fluorazepam and fluoxetine are substrates of CYP3A4, therefore, metronidazole and antifungal azolics, acting as inhibitors, may prolong and enhance the sedative effects of these agents (Grimm 2006).

Quetiapine is mainly metabolized by CYP3A4, therefore the concomitant use of the aforamentioned inhibitors may considerably affect the clearance of this antipsychotic. As a consequence extrapyramidal effects of postural hypotension may occurr (Urichuk 2008; Prior 2003; Grimm 2006).

Vasoconstrictors

Vasoconstrictors (i.e. epinephrine or levonordefrin) represent a considerable source for DDI (6 cases in 21% of drug users in our studied population) since they are widely used in dentistry to localize the injection of local anesthetic to the site of administration and to decrease local bleeding (Yagiela 1999).

Vasoconstriction occur through the stimulation of α 1 receptors in the peripheral vessels. In particular epinephrine equally stimulates α and β receptors, while levonordefrin presents a

higher selectivity for α receptor (three times as much as β1). As the result, epinephrine has less pressor effects due to opposing vasodilatatory property since the vasoconstriction mediated by α receptor in certain districts are counterbalanced by vasodilatation mediate by β2 stimulation on other vascular beds were β2 prevail such as in skeletal muscle (Hersh 2008).

β-blockers

In our study 3 patients were concomitantly treated with β-blockers, 2 with selective β-blocker metoprolol and 1 with non selective β-blocker carvedilol. When epinephrine or levonordefrin are administrate in concomitance with non selective β-blockers severe DDI may occur with a dose-related pattern (Hersh 2008; Centeno 2003; Mito 1988). Grimm 2006). Vasoconstrictors through α-stimulation may determine a pronounced vasoconstriction up to a hypertensive crisis or a cerebrovascular accident. β2 vasodilatatory and β1 cardiostimulatory effects of epinephrine are inhibited by non selective β-blockade (Hersh 2008). In contrast, a lack of significant blood pressure increase has been observed with selective β-blocker and epinephrine but not with levonerdefrin since this last agent does not stimulate β2 receptors responsible of peripheral vasodilatation (Hersh 2008; Gomez-Moreno 2009; Hjemdahl 1983; Rehling 1986). However both selective and non selective β-blockers impair the clearance of epinephrine and norepinephrine. Therefore, an initial test dose carefully injected in order to avoid intravascular administration followed by a careful monitoring of blood pressure is recommended in patients under this treatment. And if the hemostasis is not required and the procedure is relatively short, vasoconstrictors should be avoided (Hersh 2008).

Thyroid hormones

Inappropriate use of preparation of thyroid hormones may determine cardiovascular changes (Gomez-Moreno 2009) as a results of a chronic overstimulation of myocardial metabolism (Klein 1990). Therefore, adrenergic vasoconstrictors should be carefully used in patients with increased thyroid stimulation (Gomez-Moreno 2009; Yagiela 1999).

Antipsychotic agents

Another potential receptorial interference with vasoconstrictors is the use of antipsychotic such as quetiapine (in 1 patient) that is able to block α-receptors therefore, when patient is administered vasoconstrictors, β agonism effects prevail, determining increased heart rate and, in case of epinephrine, also peripheral vasodilatation with, as a consequence, orthostatic hypotension and reflex tachycardia (Sims 2007; Yagiela 1999). In addition, due to their antagonism to α-receptors, antipsychotic may considerably impair the effectiveness of vasoconstrictor (Sims 2007).

NSAIDs

NSAIDs are commonly prescribed in dentistry for postoperative pain and in our sample were related to 34 potential DDI, potentially interesting 88% of the patients under prescribed medications.

Antihipertensive agents

The treatment with NSAIDs for more than 5 days may impair the efficacy of antihypertensive drugs such as diuretics (especially loop diuretics), β-blockers and ACE inhibitors and angiotensin-receptor blockers, due to the inhibition on the production of vasodilatatory

prostaglandins responsible for the increase of renal blood flow (Hersh 2008; Becker 2007; Gibson 2007; Huston 1991).

Anticoagulant/antiplatelet treatment

NSAIDs prescription in patients using warfarin increases the risk for gastrointestinal bleeding fourfold to five fold (Becker 2008; Delaney 2007). With the exception of acetil salycilic acid, most NSAIDs presents minimal antiplatelet effects (Sims 2007; Becker 2008), but the actual concern is the risk of gastroduodenal erosion and bleeding in patients under NSAID, especially if associated with other antiplatelet treatments (i.e. ticlopidine) (Cadiou 2012).

In addition, it has been debated whether NSAIDs such as ibuprofen may impair antiplatelet effects competing with acetil salycilic acid for COX inhibition. Indeed, ibuprofen presents antiplatelet effect, though temporary, due to a reversible inhibition of COX (Catella-Lawson 2001). However, according to a randomized study, the antiplatelet activity of acetil salicylic acid was preserved during concomitant ibuprofen administration (Cryer 2005).

Metotrexate

In patients under metotrexate, NSAIDs should be used carefully, due to the relatively low therapeutic index if this drug and the potential severe side effects such as thrombocytopenia, neutropenia, renal failure. Indeed, NSAID may cause an impaired renal perfusion, thus increasing the risk for potential side effect due to a reduced metotrexate clearance (Hersh 2008; Frenia 1992).

Selective Serotonine Reuptake Inhibitors (SSRIs)

SSRIs, such as fluoxetine and escitalopram, decrease platlet aggregation due to the inhibition of the reuptake of serotonin and the downregulation of serotonin receptors also at platelet's

level and, therefore, enhance the risk of bleeding (Serebruany 2006; Hersh 2008). Therefore, the concomitant use of NSAIDs in patients under SSRI should be avoided. Indeed, the risk of gastrointestinal bleeding following NSAIDs treatment raises from 3.7-4.5 up to 15.6-16.7 in patients concomitantly under SSRI, an effect which is greater than a simple additive effect of each individual class (Dalton 2003; De Abajo 1999; Langman 1994).

Narcotic analgesics

Patients treated with opioid analgesics during conscious sedations or to manage post-procedural pain are at risk of serious DDI (Hersh 2008; Haas 1999).

In a quarter of the patients under medications, 6 potential DDI with narcotic analgesics and drugs acting on central nervous system tramadol, antipsychotics (quietapine), benzodiaepines and SSRI were detected.

Due to their depressant effects on the central nervous system the prescription of narcotic analgesic in presence of another central nervous system depressant such as other central analgesics and benzodiazepines can determine additive or supra-additive depression, excessive psychomotor impairment, sedation and uncosciousness (Hersh 2008; Sims 2007; Haas 1999).

Moreover, since opioid analgesics determine peripheral vasodilation, the may enhance orthostatic hypotension and, therefore, increase postural instability and the risk of falls in patients treated with antipsychotics with α blocking properties such as quetiapine (Sims 2007).

In patients concomitantly treated with SSRI, opiods such as tramadol and meperidine may precipitate and acute serotonin syndrome characterized by confusion, agitation, hyperthermia, diaphoresis, sinus tachycardia, tachypnea, hypertension (Sims 2007; Becker 2008).

Sedative and anxiolitics drugs

Benzodiazepine are used in dentistry practice in order to provide anxiolysis, sedation and skeletal muscle relaxation. 9 potential DDI have been found out in one third of drug users.

CNS depressants

The association of two or more CNS depressant (such as quetiapine, or other benzodiazepines) may increase the levels of central depression with excessive sedation and respiratory depression (Sims 2007).

Fluoxetine and verapamil

Fluoxetine and Calcium-channel blocker verapamil, due to inhibition of CYP3A4, may prolong the duration of sedation, inhibiting metabolism of benzodiazepines (Hersh 2008; Becker 2007; Sims 2007; Moore 1999). These combination should be avoided especially in the elderly, who are particularly sensitive to benzodiazepine sedation (Hersh 2008).

Oral anticoagulants

The oral sedative chloral hydrate, due to a displacement interaction (competition for plasma protein binding) with oral anticoagulant may cause hypothrombinemia. This effect is transient and may be clinical insignificant especially with single dose of chloral hydrate (Moore 1999).

Conclusions

The present study underlines that very often patients attending a dental clinic may be under a pharmacological treatment and polypharmacy is not unfrequent. As the population becomes older there is a subsequent raise in drug prescription and therefore in the risk of DDI.

Indeed, the importance of patients' medical histories will increase along with the number of medically complex patients who visit the dental general practice

Preoperative assessment of dental patients including a complete evaluation, documenting all the medications including within the dental record also DS and HR, enables the dentist to design a treatment plan that avoid potential DDIs. Dentists should also be informed about HR and DS that may affect efficacy and safety of dental treatment, since many consumers do not report their health care providers about them. Moreover, dentists should be aware of how patient's prescribed medications may interact upon dental treatment.

Therefore, medication profiles and potential DDI knowledge is essential for safe practice in dentistry and also represents an important base for planning undergraduate as well as postgraduate teaching in clinical pharmacology.

Tables

Table 1. Socio-demographic features of the sample population divided according to age.

Age (years)	**<15**	**15-24**	**25-34**	**35-44**	**45-54**	**55-64**	**>64**	***Tot***
Sex								
Male	28	1	5	2	4	3	13	***56***
Female	13	6	3	6	4	9	3	***44***
Total	41	7	8	8	8	12	16	***100***
BMI (kg/m2)								
(mean±SD)	19.3±2.1	20.6±2.8	23±2.4	22.6±2.4	24.7±4.7	22.9±1.9	24.6±1.6	***21.6±3.3***
Marital status								
Single	41	7	7	3	0	1	1	***60***
Married/cohabiting	0	0	1	4	8	8	12	***33***
Separated/divorced	0	0	0	1	0	0	1	***2***
Widowed	0	0	0	0	0	3	2	***5***
Place of living								
<5’000 inhabitants	12	4	1	3	2	5	3	***30***
~10'000 inhabitants	11	0	3	1	4	1	3	***23***
~20'000 inhabitants	5	1	0	0	1	3	3	***13***
>20'000 inhabitants	13	2	4	4	1	3	7	***34***
Education								
Primary school	11	0	2	3	4	4	11	***35***
Lower Secondary	4	4	1	1	2	6	3	***21***
Upper secondary school	0	3	2	3	2	2	2	***14***
Bachelor	0	0	3	1	0	0	0	***4***
None	26	0	0	0	0	0	0	***26***
Occupation								
Student	33	6	2	0	0	0	0	***41***
Retired	0	0	0	0	0	7	16	***23***
Blue collar	0	1	0	1	3	1	0	***6***
White collar	0	0	3	5	2	0	0	***10***
Unemployed	0	0	0	1	1	1	0	***3***
Self-employed	0	0	0	0	0	2	0	***2***
Housewife	0	0	1	1	0	1	0	***3***
NONE	8	0	2	0	2	0	0	***12***

Table 2. Drug use divided according to age and sex.

Age (years)	**<15**	**15-24**	**25-34**	**35-44**	**45-54**	**55-64**	**>64**	**Tot**
Drug Users (DU)								
Male								
N	6	0	0	1	2	1	13	**23**
% of Total DU	16,2	0,0	0,0	2,7	5,4	2,7	35,1	62,2
% of patients	14,6	0,0	0,0	12,5	25,0	8,3	81,3	23,0
Female								
N	0	1	1	2	3	4	3	**14**
% of Total DU	0,0	2,7	2,7	5,4	8,1	10,8	8,1	37,8
% of patients	0,0	14,3	12,5	25,0	37,5	33,3	18,8	14,0
Tot of DU								
N	6	1	1	3	5	5	16	**37**
% of Total DU	16,2	2,7	2,7	8,1	13,5	13,5	43,2	**100**
% of patients	14,6	14,3	12,5	37,5	62,5	41,7	100	37
N of Total subjects	***41***	***7***	***8***	***8***	***8***	***12***	***16***	***100***

Table 3. Potential drug-drug interaction with treatment commonly used in dentistry divided according to age and sex.

Age (years)	<15	15-24	25-34	35-44	45-54	55-64	>64	Tot
DDI								
Male								
N	0	0	0	0	8	0	41	***49***
% of total DDI	0	0	0	0	9,8	0	50,0	***59,8***
Female								
N	0	1	0	2	15	6	9	***33***
% of total DDI	0	1,2	0	2,4	18,3	7,3	11,0	***40,2***
Total DDI								
N	0	1	0	2	23	6	50	***82***
% of total DDI	0	1,2	0	2,4	28,0	7,3	61,0	***100***
DDI/DU	0	1	0	0.7±1.2	4.6±3.1	1.2±1.3	3.1±2.7	***3.4±2.5***
DU with DDI								
Male								
N	0	0	0	0	2	0	13	***15***
%	0	0	0	0	5,4	0	35,1	***40,5***
Female								
N	0	1	0	1	2	3	3	***10***
%	0	2,7	0	2,7	5,4	8,1	8,1	***27,0***
Total								
N	0	1	0	1	4	3	15	***24***
%	0	2,7	0	2,7	10,8	8,1	40,5	***64,9***
Total subjects	***41***	***7***	***8***	***8***	***8***	***12***	***16***	***100***

*data are expressed as mean ±standard deviation. DU= Drug Users; DDI= Drug-Drug Interaction

Table 4. Drug used divided according ATC classification (Part I)

	Drugs		**Users**	
	N	**%**	**N**	**%**
A - ALIMENTARY TRACT AND METABOLISM	**14**	**13,6**	**10**	**27,0**
A02 - DRUGS FOR ACID RELATED DISORDERS	*6*	*5,8*	*6*	*16,2*
A02BC01 – omeprazole	4	3,9	4	10,8
A02BC03 – lansoprazole	2	1,9	2	5,4
A10 - DRUGS USED IN DIABETES	*7*	*6,8*	*4*	*10,8*
A10AB04 – insulin lispro	1	1,0	1	2,7
A10BA02 – metformin	4	3,9	4	10,8
A10BB09 – glicazide	1	1,0	1	2,7
A10BF01 – acarbose	1	1,0	1	2,7
A12 - MINERAL SUPPLEMENTS	*1*	*1,0*	*1*	*2,7*
A12BA01 - potassium chloride	1	1,0	1	2,7
B – BLOOD AND BLOOD FORMING ORGANS	**16**	**15,5**	**15**	**40,5**
B01 - ANTITHROMBOTIC AGENTS	*15*	*14,6*	*14*	*37,8*
B01AA03 – warfarin	3	2,9	3	8,1
B01AA07 – acenocoumarol	1	1,0	1	2,7
B01AC05 – ticlopidine	2	1,9	2	5,4
B01AC06 - acetylsalicylic acid	9	8,7	9	24,3
B03 – ANTIANEMIC PREPARATIONS	*1*	*1,0*	*1*	*2,7*
B03BB01 - folic acid	1	1,0	1	2,7
C - CARDIOVASCULAR SYSTEM	**34**	**33,0**	**20**	**54,1**
C01 - CARDIAC THERAPY	*1*	*1,0*	*1*	*2,7*
C01DA14 - isosorbide mononitrate	1	1,0	1	2,7
C03 – DIURETICS	*3*	*2,9*	*3*	*8,1*
C03EA01 - hydrochlorothiazide and potassium-sparing agents	3	2,9	3	8,1
C07 - BETA BLOCKING AGENTS	*3*	*2,9*	*3*	*8,1*
C07AB02 – metoprolol	1	1,0	1	2,7
C07AG05 – carvedilol	2	1,9	2	5,4
C08 - CALCIUM CHANNEL BLOCKERS	*4*	*3,9*	*4*	*10,8*
C08CA01 – amlodipine	1	1,0	1	2,7
C08CA02 – felodipine	1	1,0	1	2,7
C08CA11 – manidipine	1	1,0	1	2,7
C08DA01 – verapamil	1	1,0	1	2,7
C09 – AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	*10*	*9,7*	*10*	*27,0*
C09AA02 – enalapril	1	1,0	1	2,7
C09AA04 – perindorpil	2	1,9	2	5,4
C09AA15 – zofenopril	1	1,0	1	2,7
C09BA07 - benazepril + diuretics	4	3,9	4	10,8
C09CA07 – telmisartan	1	1,0	1	2,7
C09DA04 - irbesartan + diuretics	1	1,0	1	2,7
C10 - LIPID MODIFYING AGENTS	*13*	*12,6*	*11*	*29,7*
C10AA01 – simvastatin	3	2,9	3	8,1
C10AA05 – atorvastatin	6	5,8	6	16,2
C10AA07 – rosuvastatin	1	1,0	1	2,7
C10AX06 – omega-3-triglycerides	2	1,9	2	5,4
C10BA02 - ezetimibe + simvastatin	1	1,0	1	2,7

Table 4. Drug used divided according ATC classification (Part II)

	Drugs		**Users**	
	N	**%**	**N**	**%**
G – GENITO URINARY SYSTEM /SEX HORMONES	**3**	**2,9**	**3**	**8,1**
G03 - SEX HORMONES/MODULATORS OF THE GENITAL SYSTEM	*1*	*1,0*	*1*	*2,7*
G03AB06 - gestodene + estrogen	1	1,0	1	2,7
G04 – UROLOGICALS	*2*	*1,9*	*2*	*5,4*
G04CB02 – dutasteride	2	1,9	2	5,4
H - SYSTEMIC HORMONAL PREPARATIONS*	**3**	**2,9**	**3**	**8,1**
H02 – CORTICOSTEROIDS FOR SYSTEMIC USE	*1*	*1,0*	*1*	*2,7*
H02AB04 - methylprednisolone	1	1,0	1	2,7
H03 – THYROID THERAPY	*2*	*1,9*	*2*	*5,4*
H03AA01 – levothyroxine	2	1,9	2	5,4
J – ANTIINFECTIVES FOR SYSTEMIC USE	**3**	**2,9**	**3**	**8,1**
J01 – ANTIINFECTIVES FOR SYSTEMIC USE	*3*	*2,9*	*3*	*8,1*
J01CA04 – amoxicillin	1	1,0	1	2,7
J01CR02 - amoxicillin + enzyme inhibitor	1	1,0	1	2,7
J01MA17 – prulifloxacin	1	1,0	1	2,7
L - ANTINEOPLASTIC/IMMUNOMODULATING AGENTS	**2**	**1,9**	**2**	**5,4**
L01 – ANTINEOPLASTIC AGENTS	*1*	*1,0*	*1*	*2,7*
L01BA01 – metotrexate	1	1,0	1	2,7
L04 – IMMUNOSUPPRESSANTS	*1*	*1,0*	*1*	*2,7*
L04AD02 – tacrolimus	1	1,0	1	2,7
M - MUSCULO-SKELETAL SYSTEM	**3**	**2,9**	**2**	**5,4**
M01 - ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	*3*	*2,9*	*2*	*5,4*
M01AE01 – ibuprofen	1	1,0	1	2,7
M01AH01 – celecoxib	1	1,0	1	2,7
M01AX17 – nimesulide	1	1,0	1	2,7
N – NERVOUS SYSTEM	**9**	**8,7**	**9**	**24,3**
N02 – ANALGESICS	*1*	*1,0*	*1*	*2,7*
N02AX52 - tramadol, combinations	1	1,0	1	2,7
N03 – ANTIEPILEPTICS	*3*	*2,9*	*3*	*8,1*
N03AX14 – levetiracetam	2	1,9	2	5,4
N03AX16 – pregabalin	1	1,0	1	2,7
N05 – PSYCHOLEPTICS	*3*	*2,9*	*3*	*8,1*
N05AH04 – quetiapine	1	1,0	1	2,7
N05BA06 – lorazepam	1	1,0	1	2,7
N05CD01 – fluorazepam	1	1,0	1	2,7
N06 – PSYCHOANALEPTICS	*2*	*1,9*	*2*	*5,4*
N06AB03 – fluoxetine	1	1,0	1	2,7
N06AB10 – escitalopram	1	1,0	1	2,7

*excluding sex hormones and insulins.

Table 4. Drug used divided according ATC classification (Part III)

R - RESPIRATORY SYSTEM	**15**	**14,6**	**12**	**32,4**
R01 - NASAL PREPARATIONS	*4*	*3,9*	*4*	*10,8*
R01AC02 – levocabastine	1	1,0	1	2,7
R01AD12 – fluticasone furoate	2	1,9	2	5,4
R01BA52 - pseudoephedrine, combinations	1	1,0	1	2,7
R03 – DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES	*5*	*4,9*	*5*	*13,5*
R03AC02 – salbtamol	1	1,0	1	2,7
R03AK06 - salmeterol/fluticasone	1	1,0	1	2,7
R03AK07 – budesonide/formoterol	1	1,0	1	2,7
R03BA05 – fluticasone	1	1,0	1	2,7
R03BB04 - tiotropium bromide	1	1,0	1	2,7
R05 - COUGH AND COLD PREPARATIONS	*1*	*1,0*	*1*	*2,7*
R05CB03 – carbocisteine	1	1,0	1	2,7
R06 - ANTIHISTAMINES FOR SYSTEMIC USE	*5*	*4,9*	*5*	*13,5*
R06AX17 – ketotifen	1	1,0	1	2,7
R06AX22 – ebastine	1	1,0	1	2,7
R06AX27 – desloratadine	3	2,9	3	8,1
V – VARIOUS	**1**	**1,0**	**1**	**2,7**
V03 – ALL OTHER THERAPEUTIC PRODUCTS	*1*	*1,0*	*1*	*1,0*
V03AE02 – sevelamer	1	1,0	1	1,0
Total	**103**	**100**		

Table 5. Potential DDIs with patients' medications (Part I)

Study patients' medications that may interfere with common dentistry drugs	N of DDI	% of DDI	N° of DU*	% of DU*
Antimicrobials				
A02BC01 – omeprazole	4	4,9	4	16,7
A02BC03 – lansoprazole	2	2,4	2	8,3
B01AA03 – warfarin	3	3,7	3	12,5
B01AA07 – acenocoumarol	1	1,2	1	4,2
C08DA01 – verapamil	1	1,2	1	4,2
C10AA01 – simvastatin	3	3,7	3	12,5
C10AA05 – atorvastatin	6	7,3	6	25,0
C10BA02 - ezetimibe + simvastatin	1	1,2	1	4,2
G03AB06 - gestodene + estrogen	1	1,2	1	4,2
L04AD02 – tacrolimus	1	1,2	1	4,2
N05AH04 – quetiapine	1	1,2	1	4,2
N05BA06 – lorazepam	1	1,2	1	4,2
N05CD01 – fluorazepam	1	1,2	1	4,2
N06AB03 – fluoxetine	1	1,2	1	4,2
Subtotal	***27***	***32,9***	***18***	***75,0***
Vasoconstrictors				
C07AB02 – metoprolol	1	1,2	1	4,2
C07AG05 – carvedilol	2	2,4	2	8,3
H03AA01 – levothyroxine	2	2,4	2	8,3
N05AH04 – quetiapine	1	1,2	1	4,2
Subtotal	***6***	***7,3***	***5***	***20,8***
NSAIDs				
B01AA03 – warfarin	3	3,7	3	12,5
B01AA07 – acenocoumarol	1	1,2	1	4,2
B01AC05 – ticlopidine	2	2,4	2	8,3
B01AC06 - acetylsalicylic acid	9	11,0	9	37,5
C03EA01 - hydrochlorothiazide and K^+-sparing agents	3	3,7	3	12,5
C07AB02 – metoprolol	1	1,2	1	4,2
C07AG05 – carvedilol	2	2,4	2	8,3
C09AA02 – enalapril	1	1,2	1	4,2
C09AA04 – perindorpil	2	2,4	2	8,3
C09AA15 – zofenopril	1	1,2	1	4,2
C09BA07 - benazepril + diuretics	4	4,9	4	16,7
C09CA07 – telmisartan	1	1,2	1	4,2
C09DA04 - irbesartan + diuretics	1	1,2	1	4,2
L01BA01 – metotrexate	1	1,2	1	4,2
N06AB03 – fluoxetine	1	1,2	1	4,2
N06AB10 – escitalopram	1	1,2	1	4,2
Subtotal	***34***	***41,5***	***21***	***87,5***

*DU=Drug Users

Note: subtotals of DU, may not correspond to the actual sum due to the fact that the same subject may use more than one drug.

Table 5. Potential DDIs with patients' medications (Part II)

Study patients' medications that may interfere with common dentistry drugs	N of DDI	% of DDI	N° of DU*	% of DU*
Narcotic analgesics				
N02AX52 – tramadol, combinations	1	1,2	1	4,2
N05AH04 – quetiapine	1	1,2	1	4,2
N05BA06 – lorazepam	1	1,2	1	4,2
N05CD01 – fluorazepam	1	1,2	1	4,2
N06AB03 – fluoxetine	1	1,2	1	4,2
N06AB10 – escitalopram	1	1,2	1	4,2
Subtotal	***6***	***7,3***	***6***	***25,0***
Sedative and anxiolitics				
B01AA03 – warfarin	3	3,7	3	12,5
B01AA07 – acenocoumarol	1	1,2	1	4,2
C08DA01 – verapamil	1	1,2	1	4,2
N05AH04 – quetiapine	1	1,2	1	4,2
N05BA06 – lorazepam	1	1,2	1	4,2
N05CD01 – fluorazepam	1	1,2	1	4,2
N06AB03 – fluoxetine	1	1,2	1	4,2
Subtotal	***9***	***11,0***	***8***	***33,3***
Total	**82**	**100**	**/**	**/**

*DU=Drug Users

Note: subtotals of DU, may not correspond to the actual sum due to the fact that the same subject may use more than one drug.

Drugs, dietary supplements, doping in sport

The legal use of medication by athletes appears to be common, though poorly investigated (Tscholl et al., 2008; Huang et al., 2006). Indeed, although young and generally healthy, athletes often use a wide variety of medication to treat illness, cure injuries and obtain a competitive edge. Besides an indirect marker of health, as aforementioned, drug use may also represent in some cases a clue of doping, such as, for instance, the use of antibiotic cream in order to counteract acne in androgenic steroids users (Walker & Adams, 2009).

DS consumption is common in sport, however, though the beneficial claimed in advertising, there is little evidence to support these contentions, since the actual advantage of supplementation on sporting performance is still controversial (Dascombe et al., 2010; Bishop et al., 2010; Maughan et al., 2007). DS are usually unnecessary if not dangerous, due to inadequate product labelling, presence of contaminants or undeclared substances (such as anabolic androgenic steroids) that may determine involuntary doping (Geyer 2008; de Hon 2007; Van Thuyne 2006; Sundgot-Borgen 2003; Pipe 2002).

In addition, besides contrasting evidence for benefits, DS use may, in itself, represent the first step to illegal preparations since it may be associated with risky behaviours such as inappropriate use of medication, excessive intake of energy drinks, or illicit performance-enhancing drugs such as anabolic steroids (AS) and other doping agents (Wiefferink et al., 2008; Papadopoulos et al., 2006).

In “Dietary supplements and doping in cycling: use, knowledge and attitude in Italian young elite athletes” I have performed a survey within élite sport, i.e. young cyclists, with the aim to investigate doping knowledge (substances, benefits and risks and diffusion) and any factors potentially associated (socio-demographic characteristics, time devoted to physical activity, use of drugs or DS). Indeed, though suspected, the use of doping within these subjects remains a quite unexplored issue.

I have also explored the setting of recreational athletes in the survey “Dietary supplements and anabolic substances in recreational sports: surveys in fitness centres in Northern Italy” aimed at collecting data concerning use and knowledge of DS and AS among recreational athletes. Indeed, even recreational athletes may often try to push the limits of their performance using performance- enhancing substances, such as DS (Guyda 2005). Moreover, the prevalence of AS in fitness sports appears alarmingly high, ranging from 5 to 14%, and represents, thus, an issue of extreme relevance for the health care system (Leifman 2011).

Dietary supplements and doping in professional athletes: a study in elite cyclists

Abstract

Dietary supplements (DS) and doping use in elite cyclists is a relatively unexplored research field. The aim of this study was to survey the attitude towards drugs and DS and to explore the knowledge concerning doping in cycling. For this purpose, an anonymous semi-structured questionnaire was administrated. 40 cyclists aged 19-23 and practicing this sport for 14-30 hour/week were interviewed. The use of drugs or DS in the last 3 months occurred in 82,5% and 97,5% of the participants respectively. 97,5% of the subjects were able to name at least 1 doping agent (range 1-10); EPO the mainly represented, was mentioned by 32 athletes (80%). Within a fixed list of 18 substances (among which 14 were doping agents), the participants recognized 3-18 of them as doping. Doping knowledge appeared to be related to a higher drug use (r^2=0.1614; p=0.01).. The main sources for doping information were internet (82,5%) and media in general (60%). Opinions about doping prevalence significantly differed among the subjects if considered cycling in general and non professional cyclers instead their own team (100%, 97,5% or 17,5%, respectively; p<0,001).These findings reveal the need for educational interventions to improve knowledge and awareness of potential dangers related to doping.

Introduction

Doping use appears to be a common practice among professional cyclists and it had been described as endemic (Lentillon-Kaestner & Carstairs, 2010; Schneider, 2006, Kimmage, 2001). Besides the intent of improving physical performance, the use of banned substances was reported to create team cohesion and identity (Lê-Germain & Leca, 2005). However, doping practice appeared to be changed, switching from a team practice to a more individualized one (Lentillon-Kaestner & Carstairs, 2010). The use of banned substances seems to be influenced both by personal attitude as well as by the social environment (doctors, coaches, teammates, friends, etc.) (Lentillon-Kaestner & Carstairs, 2010). Thus, doping can be considered not just as a sport issue but as a social phenomenon. Indeed, young cyclists, exposed to a high pressure wishing to become professional, often seek the advice of more

experienced athletes, who had probably used illicit substances during their careers (Lentillon-Kaestner & Carstairs, 2010). However, though suspected, the use of doping within the young cyclists remains a quite unexplored issue.

Dietary supplements (DS) consumption is common in sport with a prevalence among elite athletes ranging from 57% to as high as 94%, according to different authors (Lazic et al., 2011 Petróczi & Naughton, 2008; Huang et al., 2006; Baylis et al., 2001). The pattern of DS use appears to be largely sport-dependent. In particular, sports involving continuous, endurance-type activity, such as cycling, athletics and rowing, present the highest consumption of DS (Huang et al., 2006; Somerville & Lewis, 2005). Though the beneficial claimed in advertising, there is to date little evidence to support these contentions, since the advantage of supplementation on sporting performance is still controversial (Dascombe et al., 2010; Bishop et al., 2010; Maughan et al., 2007). Among athletes with a balanced diet, the risk of vitamin or mineral deficiency is rare, therefore, dietary supplementation is usually unnecessary (Sundgot-Borgen et al., 2003). Moreover, DS presents a close relationship with doping, since the use may be associated to the risk of a positive doping result due to the presence of prohibited substances not declared on the label (Geyer et al., 2008; de Hon & Coumans, 2007; Van Thuyne et al., 2006; Pipe & Ayotte, 2002). In addition, DS intake has been found to increase the likelihood of subsequent use of doping substances and may be, therefore, considered as a risk factor for doping (Suzic Lazic et al., 2011; Dascombe et al., 2010; Wiefferink et al., 2007; Papadopoulos et al., 2006).

Although young and generally healthy, athletes often use a wide variety of medication to treat illness, cure injuries and obtain a competitive edge. Drug consumption may also represent an indirect marker of disease serious enough to require medical treatment, as well as in some cases a clue of doping if considering, for instance, those used to counteract typical doping adverse reactions, i.e. antibiotic cream for acne in androgenic steroids users (Walker & Adams, 2009). Nevertheless, the legal use of medication by young athletes has so far received little attention, even if some studies reported prevalence around 44-61% (Tscholl et al., 2008; Huang et al., 2006).

Effective doping prevention strategies need to consider doping awareness and attitudes as well as the frequency and patterns of use of medications and DS. The aim of the present investigation was therefore to gain insight into use and attitudes towards doping, drugs and DS among Italian young elite cyclists. For this purpose, DS as well as drug use were surveyed within the sample. Doping knowledge (substances, benefits and risks and diffusion) and any

factors potentially associated (socio-demographic characteristics, time devoted to physical activity, use of drugs or DS) were investigated.

Methods

Participants

The investigation was conducted from July to August 2009, during race periods, among non professional élite-under 23 cyclists. Five teams were involved, all from Northern Italy: 2 from Lombardy, 2 from Piedmont and 1 from Veneto. Informed consent was obtained from all participants and the survey was conducted in accordance with ethical research guidelines.

Questionnaire

A semi-structured, anonymous questionnaire with multiple choice close and open answers was designed to gather the following data:

- socio-demographical characteristics: age, education, place of living;
- anthropometrical (height, weight);
- information concerning cycling: time devoted, since how many years it had been played and if it was a full time activity;
- information about the use of drugs within the last three months: reason for using and sources for information/prescribing;
- information about the use of DS within the last three months: reason, frequency of use, expected and obtained benefits, and sources for information;
- knowledge of doping agents: ability to name doping agents and to recognize them among a fixed list of substances, opinion concerning use and diffusion in cycling in general, among elite-under 23 team and in their own team, reasons for using doping, risks related and sources for information.

Data analysis

Collected data were inserted in a digital archive and analyzed through a descriptive approach. Data were expressed as mean±standard deviation (SD). Anthropometric data, height and weight were expressed as body mass index (BMI, kg/m^2). Prescribed drugs were codified according to the WHO Anatomical Therapeutic Chemical (ATC) classification system (http://www.whocc.no/atc/structure_and_principles/). Statistical significance of the results

was examined using the χ^2-test distribution, the unpaired t-test, ANOVA or the Pearson correlation test, as appropriate

Results

Participants

Forty elite-under-23 cyclers all male were interviewed. Anthropometric and socio-demographic features in the sample considered are presented in Table 1.

Prescription drugs

30 subjects (75,0%) have used, in the last 3 months, 84 drugs, 2,8±1,0 drugs/person (range: 1-5). In addition, 6 DS and 1 omeopathic product (damiana compositum) were included by mistake by 4 subjects among prescribed drug. The most common ATC group prescribed was group B "Blood and blood forming organs": 31 prescriptions (36,9%) in 22 subjects (73,3%). The complete list of drugs grouped according to ATC is shown in table 2. Among the heterogeneuos group of active principles, the most common were V03AB32 glutathione (15, 17,9% of all prescriptions, used by 50,0% of subjects), followed by the antianemic preparation BA03BA cyanocobalamin (10, 11,9% of all prescriptions, used by 33,3% of subjects). The most common class of drugs was NSAIDs (M01A and N02B), with 14 prescriptions (16.7%) reported by 10 subjects (33.3%).

When provided (96,4% of subjects), reasons for using drugs were "vitamin deficiency" (27, 32.1%), "energy recovery" (18 cases, 21.4%) , "detox" (12, 14,3%), "fever/influence" (7, 8.3%), "unease" (5, 6.0%), "anaemia" (5, 6.0%), "pain" (4, 4.8%), "to maintain hematocrit" (4, 4.8%), "allergy" (2, 2,4%), "fitness maintainence" (1, 1.2%).

Dietary supplements

39 participants (97,5%) declared to have used DS in the previous 3 months. A total of 108, 2,8±1,3 DS/person (range: 1-5), were used cyclically (47, 43,5%), daily (37, 34,3%), on demand (17, 15,7%), during race (5, 4,6%) and the most frequently used were aminoacids. In table 3 the complete list of DS use are presented. In addition, an omeopathic product (damiana compositum) was also listed among DS.

When reported (92,6%), reasons for DS use were "to integrate a dietary deficiency" (53, 49,1%), a "better recovery" (38, 35,2%), "wellness" (5, 4,6%) and "better reactions" (4, 3,7%)

Benefits were observed among 27 users (69.2%) and were represented by “a better recovery” (16, 59,3%), “wellness” (6, 22,2%), “more strength” (4, 14,8%) and cramp prevention (1, 3,7%).

Doping

38 (95,0%) subjects were able to name at least 1 agent considered as doping, for a total of 118 (3,2±2 doping agent/individual; range: 1-10) and the most commonly mentioned one was erythropoietin (32, 27,1% %) (Table 4). In three cases were listed also non doping agents, i.e, tramadol in 2 (1,7%) cases and sildenafil in 1 (0,8%).

Subjects were also asked to identify the known substances within a fixed list and to discriminate if they were doping or not (Table 5). The list included 18 agents, among which 14 of them were doping according the 2009 WADA list. The surveyed subjects correctly identified a mean of 10,6±3,7 substances (range: 3-18), among which 7,6±2,7 (range: 3-14) were properly identified as doping agents. Among the most frequently recognized (by 39 out 40 subjects), growth hormone and testosterone, were considered doping agents in 100% of the cases, while amphetamine in 94,8%, and within non doping agents, tramadol in 6 out of 25 cases (24.0%). Phenmetrazine was the less recognized substances, since it was known by only 2 (5,0%) participants and was considered as doping in both cases. On the other side, probenecid and albumin, known by 5 (12,5) and 17 (42,5%) subjects respectively, were recognized as doping agent only in 40,0% and 52.9% of cases.

According to the majority of the surveyed (38, 95%), doping agents were globally dangerous with potentially serious consequences, while for 2 of them only erythropoietin, Continuous Erythropoietin Receptor Activator (CERA) erythropoietic agents and psychotropic agents were actually unsafe.

Reasons given to explain doping use were “advantages in terms of physical performance” (23, 57,5%), “results achieved in a short time” (16, 40%), “good results during the competition” (15, 37,5%), “because it’s a common habit" (3, 7,5%) and other (2, 5%).

Opinions about doping prevalence significantly varied according the participants if it was considered cycling in general and non professional cyclers instead their own team (100%, 97,5% or 17,5%, respectively; $p<0,001$); the opinion about the degree of diffusion significantly differed as well (table 6).

Sources of information

As presented in table 7, the several kind of sources of information were differently represented ($p<0.0001$) if the topic was doping instead of medications or DS. Indeed, in the last two cases, the prevalence of the different sources was quite homogeneous and did not statistically differ. In particular, the main sources of information were for drugs and DS the "specialized doctor" in 90,0% and 74,4%, respectively, while in the case of doping were principally represented by internet (82,5%) and newspapers/radio/tv (60%).

Correlations

No relationship between socio-demographic or anthropometric pattern were found with drug as well as DS use (not shown) or with doping knowledge.

The knowledge of doping (evaluated as the ability to name prohibited substances as well as to identify doping agents) was significantly related with the number of drug used ($r^2=0.1614$; $p=0.01$) but not with DS ($r^2=0.0068$; $p=0.61$).

Discussion

To our best knowledge, this is the first study investigating the use of DS and medicines in young elite cyclists and its relationship with knowledge and attitudes towards doping. Participants were all young (age range: 19-23 years), healthy and with good instruction levels (97,5% with at least secondary school degree), which raise even more concern on our results. Moreover, our findings show the occurrence of extremely high use of prescription drugs as well of DS.

Indeed, the use of prescription drugs was higher than the prevalence reported in literature (44-61%) (Tscholl et al., 2008; Huang et al., 2006), since 75% of the sample have used at least one drug (up to 5) in the last 3 months, with a mean of almost 3 drugs/subject. These findings are considerably high if compared to OSMED report according to which around 50% of the general Italian male population of the same age (15-24) have used at least one drug per year (rapporto OSMED 2009).

According to our results the most popular class of drugs was represented by NSAIDs whose prevalence was similar to those observed in other surveys (33-38%), involving one third of the sample. This high prevalence may reflect conditions such as musculo-skeletal inflammation, overuse syndromes (tendinopathies) and the of pain relief for a variety of issues, which are quite common in endurance sports such as cycling (Huang et al., 2006:). Hard,

prolonging training loads without a sufficient recovery time may concur to these conditions and consequent NSAID use (Alaranta et al., 2008; Thuyne & Delbeke 2008; Tsitsimpikou et al, 2004; Huang et al., 2006; Corrigan et al., 2003) and especially top athletes have been reported to have a higher intake of medication than non-competing athletes (Dascombe et al., 2010; Tscholl et al., 2008).

ATC group B was the most common prescribed in our sample, in nearly three quarter of the subjects, a prevalence considerably far from the general population (less than 5%; OSMED report). If considered alone, iron use is mentioned as medication or a DS in nearly 30% or 15% of the subjects respectively, prevalence that are in accordance to those of around 20% reported in literature (Huang et al., 2006).

The high proportion of non-medical reasons for use of prescription drugs underlines the risk of inappropriate and excessive use of medications that could increase the risk of adverse drug events and interactions (Suzic Lazic et al., 2011). This also go in pairs with the pattern of DS use.

Indeed the data of the present study are similar to previous works (75-90%; Suzic Lazic et al., 2011; Dascombe et al., 2010) suggesting that the majority of elite athletes consume DS since almost all surveyed subjects (98%) have used at least one. Vitamins and minerals were the most commonly used DS in sports in general (50-63%; Huang et al., 2006; Lazic et al., 2011; Tsitsimpikou et al., 2004; Froiland et al., 2004; Sobal & Marquart, 1994), while in our sample of élite cyclers, aminoacids (34%) were the preferred substances.

DS were mainly used with a cyclically pattern, principally for a dietetic integration and the 60% of the users perceived benefits. Performance enhancement, extra energy supply, maximise recovery, nutritional deficiency, prevention of illness and to maintain health are major reasons offered to justify DS use (Dascombe et al., 2010; Huang et al., 2006; Froiland et al., 2004).

The present study underlines the widespread perception of DS as substitutes to normal, well-balanced diet as well as of significant benefits associated with dietary supplementation. Almost 70% of our sample was satisfied by DS use, however, though some DS could enhance the athletic performance, the scientific evidence confirming this benefit are lacking (Lazic et al., 2011; Tscholl et al., 2008; Baylis et al., 2001; Telford et al., 1992).

Moreover, DS may present unwanted side effects starting from the micronutrient levels that exceeds the safe upper level to the interactions with concomitant medications (Sundgot-Borgen et al., 2003). In addition, DS can be a source of unintentional doping, since some may

contain unlabelled substances that are included in the List of Prohibited Substances of the World Anti-Doping Agency (Geyer et al., 2008; de Hon & Coumans, 2007; Van Thuyne et al., 2006; Pipe & Ayotte, 2002). The risk is particularly high for products with lack of controls such as coming from internet sales (Fouillot, 2004). Moreover the consumption of DS has been related with a higher propensity of positive doping violations (Lazic et al., 2011; Dascombe et al., 2010; Wiefferink et al., 2007; Papadopoulos et al., 2006).

Doping

A limited knowledge about doping agents was observed in our sample, considering the low average of doping agents spontaneously named (3 per individual) or recognized from the list (50%). As expected, the most popular were the erythropoiesis stimulating agents (though Hematide was known by a few percentage, 18%, and recognized as a doping agent only by 5 out 40 cyclers), common banned substances used in cycling (Lentillon-Kaestner et al., 2011). The other substances, though spontaneously mentioned (table 4) by a few number of athletes, were mainly represented by GH (61%), stimulants (10%), testosterone or other anabolic steroids (10% or less). Moreover, less than 10% of the sample mentioned prescription drugs (insuline and corticosteroids, in 8 and 5%, respectively) as potential doping agents, while, for istance antiasthma and diuretics or other masking agents were not present in table 4. This restricted knowledge may be also observed within the list of doping substances recognized (Table 5), where, for instance, salbutamol was considered as doping by half of the cyclers and albumine probenecid, a masking agent, only by 9 and 2 out 40, respectively.

Moreover, sildenafil as well as tramadol were erroneously believed as banned substances. Pseudoepherdrine/ceterizine, commonly used for rhinitis and allergy, was known by half of participants and was considered as doping by 5% of the athletes. Noteworthy, the year of the survey, pseudoephedrine was simply included in the Monitoring Program, while, starting from 2010, it has been considered by WADA as a prohibited substance.

The non-medical sources as the main origin of information about doping should be responsible for this partial and sectorial (i.e. used in cycling) knowledge about doping.

However, though the main source of information both for drugs and DS, differently form literature (teammate or the coach; Juhn et al., 2003) was reported to be the specialized doctors, one omeopathic product (damiana compositum) was taken for a drug as well as a DS, not all the prescribed drugs were clearly specified (i.e. antibiotics) and 6 DS were included in the list of drug used.

These features reveal a certain confusion about the terminology and, together with the findings concerning doping knowledge previously discussed, underline the risk for unintentional doping using faked DS, prescribed medications or drugs used with non-medical indication (i.e. suggested by a teammate or by the coach).

95% of the cyclists were aware about the risk of doping, while 5% tried to minimize the risk of doping restricting it to some agents such as erythropoiesis stimulating and psychotropic agents.

Moreover, an apparent uneasiness when asked to express personal opinions about the occurrence of doping in cycling was observed in our sample, since the athletes declared that doping was widespread in cycling in general and at amateur level, however, when referring to their own team, the denial policy was extremely diffused since only 17,5% admitted its diffusion in their team. Indeed, although, anonymity may increase the truthfulness of the data collected, the limit of our questionnaire survey is that data are self-declared.

Interestingly, medications and DS mainly used (group B and iron), together with frequent drug use indications such as "anemia" as well as "to maintain hematocrit", underlie the particular attention towards hematocrit values within cyclers. Moreover, the significant correlation between use of prescription drugs and doping knowledge (especially represented by erhytrhopoiesis stimulating agents, very common in cycling), fatherly suggest that higher medication-users were potentially closer to doping risk.

Conclusions

The collected data confirms that a large number of athletes use DS in hope of improving performance, though often uncritically, despite the lack of evidence of their efficacy and the recognition that such practices may carry risks (toxicity issues, drug interactions, possibility of "inadvertent" doping).

In addition, superficial and "hematic-oriented" doping together with a potential hidden use, suggested by "denial policy" have been observed in our sample.

The results of the present study, therefore, provide the basis for direct interventions aimed at increasing the knowledge and awareness of the risks in doping in younger cyclers through educational and preventive programs. Indeed, nowadays, according to some authors, doping practice in cycling has become more individualized and less institutionalized one. Cyclists, therefore, have been given more power in the choice to use doping agents, with less involvement of the physicians, with a progressive rising of underground market such as

internet (Lentillon-Kaestner et al., 2011). Moreover, educational programs should also include DS and prescripted medications, (since they are strictly related to a higher propensity towards doping) as well as the consequences of their inappropriate use such as adverse reactions and involuntary doping.

Tables

Table 1. Anthropometric and socio-demographic features of the sample population.

	Total
	mean±SD (range)
Age	20.7±1.3 (19-23)
BMI (kg/m^2)	21,1±1,0 (19.5-22.9)
Hours/week	21.8±4.3 (14-30)
Started cycling (years)	11.1±3.2 (4-17)
Education	
Primary school	1 (2,5)
Secondary school	38 (95.0)
Bachelor	1 (2.5)
Non students	24 (60.0)
Students	16 (40.0)
Total	40 (100)

Table 2. Pattern of drug prescription according to the ATC classification system.

ATC	***Drug***	***Drugs***		***Users***	
		N	***%***	***n***	***%***
A*		***11***	***13,1***	***9***	***30,0***
A11AA	Multivitamins with minerals	1	1,2	1	3,3
A11DB	Group B vitamin	4	4,8	4	13,3
A11GA01	Vitamin C	1	1,2	1	3,3
A11JA	Combinations of vitamins	5	6,0	5	16,7
B		***31***	***36,9***	***22***	***73,3***
B03AA07	Ferrous sulphate	7	8,3	7	23,3
B03AB19	Sodium ferrigluconate	2	2,4	2	6,7
B03BA01	Cyanocobalamin	11	13,1	11	36.6
B03BA51	Cyanocobalamin combinations	7	8,3	7	23,3
B03BB01	Folic acid	4	4,8	4	13,3
J*		***1***	***1,2***	***1***	***3,3***
J01	Antibacterials for systemic use	1	1,2	1	3,3
M		**8**	**9,5**	**8**	**26,7**
M01AE03	*Ketoprofen*	5	6,0	5	16,7
M01AX17	*Nimesulide*	3	3,6	3	10,0
N		**7**	**8,3**	**7**	**23,3**
N02AX02	Tramadol	1	1,2	1	3,3
N02BA01	Acetylsalicylic acid	5	6,0	5	16,7
N02BE01	Paracetamol	1	1,2	1	3,3
R		***3***	***3,6***	***2***	***6,7***
R03CC02	Salbutamol	1	1,2	1	3,3
R05CB01	Acetylcysteine	1	1,2	1	3,3
R06AE09	Levocetirizine	1	1,2	1	3,3
V		***23***	***27,4***	***20***	***66,7***
V03AB32	Glutathione	19	22,6	19	63,3
V03AF04	Calcium levofolinate	4	4,8	4	13,4
Total		***84***	***100***	***30***	***100***

* information supplied with the questionnaires did not allow identification of individual drugs

Table 3. List of dietary supplements used

	Products		**Users**	
	N	**%**	**n**	**%**
Aminoacids	37	34,3	28	71,8
Hydro saline supplement	36	33,3	28	71,8
Vitamins	19	17,6	19	48,7
Iron	6	5,6	6	15,4
Caffeine	5	4,6	5	12,8
Proteins	2	1,9	2	5,1
Ergogenic products	1	0,9	1	2,6
Total	***108***	***100***	***39***	***100***

Table 4. List of substances spontaneously mentioned as doping agents

Substance	**N**	**% respondents**
Erythropoietin	32	84,2
Growth hormone	23	60,5
CERA	26	42,1
Amphetamine	10	26,3
Testosterone	10	26,3
Gonadotropin	5	13,2
Nandrolon	5	13,2
Ephedrine	4	10,5
Insulin	3	7,9
Anabolic steroids	2	5,3
Corticosteroids	2	5,3
Tramadol*	2	5,3
Cocaine	1	2,6
Corticotropin	1	2,6
Methamphetamine	1	2,6
Sildenafil*	1	2,6

* non doping agents

Table 5. List of substances to be recognized and discriminated as doping or non doping (defined according the WADA list 2009)*

Agents	**Recognized**		**Considered**	**as doping**
	N	**%**	**N**	**%**
Doping agents				
Growth hormone	39	97,5	39	100
Testosterone	39	97,5	39	100
Amphetamine	39	97,5	37	94,9
Cocaine	33	82,5	28	84,8
Ephedrine	32	80	30	93,8
Human chorionic gonadotropin	28	70	27	96,4
Nandrolone	24	60	24	100
Salbutamol	23	57,5	21	91,3
Methadone	19	47,5	16	84,2
Albumin	17	42,5	9	52,9
Corticotropin	7	17,5	7	100
Hematide	7	17,5	5	71,4
Probenecid	5	12,5	2	40,0
Phenmetrazine	2	5,0	2	100
Non doping agents				
Paracetamol	37	92,5	0	0
Nimesulide	29	72,5	0	0
Tramadol	25	62,5	6	24,0
Pseudoephedrine*/cetirizine	20	50,0	1	5,0

* Pseudoephedrine, included in the monitoring program in 2009, has been considered doping agent by WADA since 2010.

Table 6. Opinion about use and diffusion of doping in cycling.

Does doping occurs in...	**cyclers in general? (A)**		**non-professional cyclers? (B)**		**your team? (C)**		***P* values**		
	n	**%**	**N**	**%**	**n**	**%**			
	40	100	39	97.5	7	17.5			
							A vs B	**A vs C**	**B vs C**
							0.08	<0.0001	<0.0001
- "a few"	0	0	0	0.0	6	85.7			
- "somewhat"	14	35	21	53.8	1	14.3			
- "a lot"	23	57.5	18	46.2	0	0.0			
- "every one use it"	3	7.5	0	0.0	0	0.0			

Table 7. Sources of information for drug use, DS and doping

	Drugs (A)	**DS (B)**	**Doping (C)**		**P values**	
Sources	**%**	**%**	**%**	**A vs C**	**B vs C**	**A vs B**
				<0.0001	<0.0001	0.47
Trainer	6.7	15.4	15.0			
Pharmacist	3.3	12.8	5.0			
Newspapers/radio/TV	3.3	7.7	60.0			
Internet	13.3	15.4	82.5			
GP	23.3	15.4	10.0			
Specialized doctor	90.0	74.4	20.0			
Relatives/friends	6.7	15.4	35.0			

Dietary supplements and anabolic substances in recreational sports

Abstract

Purpose: To collect data concerning use and knowledge of dietary supplements (DS) and anabolic substances (AS) among recreational athletes.

Methods: Anonymous semi-structured questionnaires were distributed to generic fitness centre visitors and to bodybuilders. Prevalence, knowledge, attitudes and factors related to DS or AS intake were investigated. Selected bodybuilders admitting the use of AS underwent anonymous interview.

Results: Among fitness centre generic visitors, 50 respondents aged 29.5±6.5 years (94.0% males, main activities: fitness, 40% and bodybuilding, 24%) reported DS use in 82.0% cases (2.4±1.3 DS/subject), mainly aminoacids (36.7%) and proteins (28.6%). 78.6% perceived DS use as satisfactory. No association was observed between socio-demographic features and use/attitudes towards DS. DS intake was considerably higher in bodybuilding (3.1±1.5 vs 2.0±1.5 DS/subject; $P<0.05$).

Among bodybuilders, 31 (83.9% males) aged 31.2±7.7 years, completed the questionnaire. 54.8% of respondents (100% males, $P<0.03$ vs females) named at least one AS (2.9±1.6/subject), mainly testosterone and nandrolone. In a list of 21 AS-related adverse reactions, 13.1±5.2 were not recognized. Although none declared AS use, some (25.8%) admitted previous consideration.

According to anonymous interviews to 7 admittedly AS users (100% males; age 36.3±8.2 years), "cardiovascular problems" and "hepatotoxicity" were the main reported (57.1%) risks to AS use. Expected benefits (appearance/performance improvement) were satisfied and only two mild adverse reactions were reported.

Conclusions: DS are widespread and perceived as useful within our sample of recreational athletes. Results confirm the widespread interest in DS and in AS among bodybuilders, who however seem to have very limited and selective perception of AS-related risks.

Introduction

Over the last decade, performance- and image-enhancing substances, such as dietary supplements (DS) as well as anabolic substances (AS), have been increasingly used also outside the elite world of sport (Guyda 2005; Huang, 2006; Kanayama 2001).

DS use appears to be spread also in the general population and, especially in gyms among non professionals sportsman (Guyda, 2005), since they do not require prescription and are available with claims ranging from for self-care, to increase endurance, energy and decrease fatigue, to gain muscle mass, to lose fat, etc. (Braun 2009; Tsitsimpikou 2009; Tscholl 2008; Sobal 1994; Molinero 2009). Though the intense marketing and promotion, only a few rigorous studies have been performed, therefore, the advantage of supplementation on sporting performance is controversial and the actual efficacy of most DS available on the market has been never assessed (Dascombe 2010; Bishop 2010; Maughan 2007). A balanced diet usually effectively meets all the needs of physical exercise, therefore, DS are usually unnecessary if not dangerous, due to inadequate product labelling, presence of contaminants or undeclared substances (such as anabolic androgenic steroids) (Geyer 2008; de Hon 2007; Van Thuyne 2006; Sundgot-Borgen 2003; Pipe 2002).

DS consumption has also been found to increase the likelihood of subsequent use of illicit substances, mainly represented by AS (Suzic Lazic 2011; Dascombe et al., 2010; Wiefferink et al., 2008; Papadopoulos et al., 2006). Indeed, the prevalence of drugs such as AS to improve sports performance and body appearance in fitness sports appears alarmingly high, ranging from 5 to 14%, and represents, thus, an issue of extreme relevance for the health care system (Simon 2006; Korkia 1996; Korkia 1997; Kanayama 2001; Striegel 2006; Leifman 2011). The current knowledge about the actual use and attitudes towards DS and AS among recreational athletes, such as fitness centres visitors, is however scarce (Leifman 2011; Tsitsimpikou 2011; Bojsen-Møller 2010; Oliver 2008; Chłopicka 2007; Papadopoulos 2006; Morrison 2004). Fitness centres visitors nonetheless represent a large and heterogeneous population, and educational and preventive measures aimed at reducing the improper use of substances in such population are therefore of critical importance at the individual as well as at the societal level.

We hereafter report the results of a series of independent and complementary studies among people attending fitness centres, aimed at assessing prevalence, knowledge, attitudes and factors associated to the use of DS and at surveying knowledge and risk perception related to AS use. As a whole, we observed a widespread interest in DS and AS by fitness centre

visitors and in particular among bodybuilders, as well as a very limited and selective perception of related risks. The present results may help planning educational programmes specifically targeted to carry out effective preventive strategies.

Materials and methods

Informed consent was obtained from all participants and the surveys were conducted in accordance with ethical research guidelines.

Study 1 - Dietary supplements

In January 2009 anonymous semi-structured questionnaires were distributed to clients of a gym located in Northern Italy. The three sections in the questionnaires allowed to gather:

- socio-demographical characteristics: age, sex, body mass index (BMI), education, place of living;
- information about physical activities: main physical activity, role (athlete, trainer), level, from how many years, other physical activities and total time devoted to sport;
- information about the use of DS: knowledge, use in the last three months and kinds of DS, expected and obtained benefits, sources of information and of supply.

Study 2 - Anabolic substances

The study included non-professional bodybuilders in another fitness centre in Northern Italy. Surveyed subjects were given an anonymous semi-structured questionnaire to collect the following data:

- socio-demographical characteristics: age, sex, education, place of living;
- physical activity performed, other physical activities and level and total time devoted to sport;
- knowledge about AS: acquaintance, source of information, risk perception (seriousness and adverse reaction known within a list), opinion about the diffusion among bodybuilders, reason for use and personal use.
- Drug used in the last three months: reasons and source for advice.

Study 3 - Subjective reports from AS users

This study, performed in the same fitness centre of study 2, was based on a different group of bodybuilders who, during preliminary contacts, had admitted current or previous use of AS.

The semi-open face-to-face interviews were conducted by one of the authors (GP), who has many years of experience in training at fitness centres and has a good understanding of the bodybuilding environment. The anonymous interview was carried out as a conversation in which open-ended questions were used to cover the following areas:

- Socio-demomographic data (age, kind of work)
- bodybuilding (from how many time they started and level of competition)
- knowledge of AS (definition, source of information, risks)
- use of AS (kind of AS used, reasons, benefits, adverse reactions)
- use of DS and drugs

Statistical analysis

Collected data were recorded in a digital archive (MS Excel, Microsoft Inc., USA) and analyzed through a descriptive approach. Anthropometric data (height and weight) were summarized as body mass index (BMI, kg/m^2). Statistical significance was examined using the χ^2-test distribution, the unpaired Student's *t*-test, ANOVA or the Pearson correlation test, as appropriate. Results are shown as mean±standard deviation (SD).

Results

Study 1

Subjects

A completed questionnaire was provided by a total of 50 respondents, principally males (47, 94.0%), with a mean age of 29.5±6.5 years (range: 18-44 years), and a mean BMI of 24±2.1 kg/m^2 (range: 19.7-30.1). Characteristics of the study population are represented in table I.

Sport activities

Sports were played at amateur level in the majority of the cases (41, 82.0%; 40 out 47 males, 85.1%; 1 out 3 females, 33.3%) and there were only 5 (10.0%) regional professionals (all males) and 4 (8.0%) national professionals (2 out 47 males, 4.3%; 2 out 3 females, 66.7%). Hours/week globally devoted to physical activity were 9.6±6.1 (range 3-35), 9.1±5.2 (3-35) in males, 18.6±6.7 (6-35) in females. Main sports performed were fitness (a total of 20, 40.0%; males: 19 out 20), bodybuilding (12, 24.0%; all males) and soccer (6, 12.0%; all males), and

had been practised since 10.0±7.5 years (range: 10-25), 10.1±7.6 (1-25) in males, 8.8±7.3 (1-13) in females. Participants were principally athletes (44 subjects, 88.0%; 40 out 47 males, 85.1%; 1 out 3 females, 33.3%), while only 12.0% (all males) were trainers. 44 subjects (88.0%) practised at least another sport (2.0±1.1 sports/subject; range: 1-5), 41 males (87.2%) (2.0±1.1 sport/subject; range: 1-5) and all the females (1.3±0.6 sport/subject; range: 1-2). No significant differences in sport activities were observed between males and females.

Dietary supplements use and knowledge

The majority (42, 84.0%) of the subjects (40 males, 2 females) used a total of 98 (2.3±1.3 DS/subject; range: 1-6) principally aminoacids (36, 36.7% of total DS) proteins (28, 28.6%) and creatine (13, 13.3%). DS intake was defined as continuous by 31 subjects (73.8%) and occasional in the remaining cases. No significant differences were noticed in the type of DS used among different sports played. DS were usually purchased at specialized shops by 21 users (50.0%) , fitness centre (11, 26.2%), acquaintances (11, 26.2%), internet (4, 9.5%), drugstores (2, 4.8%). DS were used principally upon advice from trainer (28 cases, 66.7%), relatives/friends (14 cases, 33.3%), physician (6, 14.3%), self-prescription (5, 11.9%), pharmacist (3, 7.1%).

The expected benefits were generally perceived as satisfied (78.6%), among these, “quicker recovery” (26 users, 61.9%) and “better performance” (17, 40.5%) were the most commonly reported. Moreover, 76.2% of the users were prone to take them again.

A satisfactory definition of DS was given by 11 (22.0%) of participants.

According to the 8 non-users of DS, “DS are necessary only for professional athletes and are related to a deep interest for health” for 5, “are useless or even dangerous” for 2 and “useful for deficiencies of the modern diet” for one.

Correlations

No association was observed between age, sex, education, place of residence and knowledge, use or attitudes towards DS. DS intake was however significantly higher in subjects practising bodybuilding in comparison to fitness, the other most represented physical activity, as well as to the other physical activities taken as a whole (3.1±1.5 DS/subject vs 2.0±1.0 or 2.0±1.1 DS/subject respectively; $P<0.05$).

Study 2 – Bodybuilders and AS

Subjects

31 subjects, 26 (83.9%) males, aged 31.2±7.7 years (range: 20-49), completed the questionnaire. Characteristics of the sample as well as data concerning physical activity are reported in table II.

AS knowledge, risks and diffusion

26 subjects (83.9%) were able to give a satisfactory definition of AS, however 23 (74.2%) identified AS only as doping agents, while only 3 (9.7%) knew also their clinical indications. 17 (54.8%), all males ($P<0.03$ *vs* females), named 44 substances, 2.9±1.6/ subject (range: 1-6), principally testosterone (12, 27.3%) and nandrolone (12, 23.7%), followed by GH (5, 11.4%), stanozolol (4, 9.1%), methandrostenolone (3, 6.8%) and danazole (2, 4.5%). 6 non AS were also erroneously included in the list: EPO (2, 4.5%), cocaine (1, 2.3%), "proteins" (1, 2.3%), creatine (1, 2.3%) and cortisone (1, 2.3%).

Though all the subjects declared to be aware about the potential risk due to the use of AS, 2 (6.5%) believed that this risk was associated only to some of them. Among a fixed list of AS-related adverse reactions, only 9.9±5.2 (range: 2-20) items were recognized as potential adverse reactions to AS and the most represented was testicular atrophy (25, 80.6%), followed by erectile dysfunction (24, 77.4%), myocardial ischaemia (23, 74.2%), liver cancer (22, 71.0%), (Table III).

Information concerning AS were collected from internet (17, 54.8%), trainer (15, 48.3%), media (14, 45.2%), acquaintances (5, 16.1%), pharmacist (1, 3.2%), or other sources (2, 9.7%).

According to 20 responders (64.5%), AS use was a widespread habit also among amateurs while for 9 (29.0%) it occurred only among professionals bodybuilders. Aesthetic reason is the main driver (28, 90.3%) reported for AS use, followed by the desire to get quicker results (21, 67.7%), to compete in a professional contest (13, 41.9%), to be advantaged in the competition (10, 32.3%), since many use them (4, 12.9%) or the risks are underestimated (1, 3.2%). Although all the subjects denied having ever used AS, 8 (25.8%) admitted that they had considered the possibility.

Drug use

8 (25.8%) declared having used a mean of 1.9±1.1 drugs in the last 3 months, a total of 15 drugs, represented by NSAIDs in 7 cases (46.7% of drugs), antiasthmatics in 4 (26.7%), oral antibiotics in 3 (20.0%) and antiulcer in 1 (6.7%). Drugs were taken under the advice of the general practitioner (7, 87.5%), pharmacist (6, 75.0%), specialized doctor (3, 37.5%), trainer (2, 25.0%).

Correlations

With the exception of the ability to name AS, reported only by male subjects, no significant relationship between knowledge of AS and level of education and other socio-demographic characteristics or drug use has been found.

Study 3 – Subjective reports from AS users

7 bodybuilders, all male, age 36.3±8.2 years, admitting the current or past use of AS, underwent anonymous interviews about knowledge and use of AS, drugs and DS.

Case 1

Sociodemographic data and bodybuilding

38 year old, had started bodybuilding 5 years before at non professional levels.*AS knowledge*

"AS", according to the subject, were "chemical products that help to increase body strength beyond the physiological possibility, some of them without increasing body mass".

He was aware of the risk for cardiovascular, liver, kidney, and prostate damage, and for impotence and alopecia.

The reported sources of information were gym mates and trainer and, in particular, self documentation through internet.

AS use

He started AS when he was 35 with the goal to improve his body appearance. AS use was based principally on self-prescription and information collected through a specialized forum on internet, chatting with long-time AS users.

He used several kinds of AS, included insulin and clenbuterol and 8 anabolic androgenic steroids (i.e. testosterone propionate, nandrolone, stanozolol, boldenone, trenbolone, drostanolone, metenolone, mesterolone) with a cyclical pattern (4-8 weeks). He had also used stimulants such as ephedrine.

He reports huge benefits such as an increase of muscular body mass of 20 kg and a consequent considerable improvement in power lifting of 100% were reported after he had started AS. Adverse reactions consisted only in mild acne.

DS or other drugs use

AS cycles were associated to proteins (3,5 g for Kg of body weight) and sometimes also to stimulants such as ephedrine. Antiestrogens and gonadotropins were used at the end of the cycles.

Case 2

Sociodemographic data and bodybuilding

He was 26-years old and had started bodybuilding at non professional level at the age of 22, to improve his body appearance.

AS knowledge

AS were defined as substances that help to improve physical performances and muscular mass. The curiosity about AS has risen talking about them with some friends. He told to be aware that AS were related to some risks, but he mentioned only impotence and sterility admitting to have a limited knowledge about other potential adverse events.

AS use

He had started AS use the year before in order to improve his body appearance and to increase the muscular mass to be as fit as the colleagues were. Under a colleague's supervision, he started to use anabolic androgenic steroids such as stanozolol, nandrolone, testosterone and trenbolone, with a cyclic pattern (for 8 weeks followed by a short stop). He reported that the expected benefits were fulfilled and did not notice any adverse reaction.

DS or other drugs use

During the AS cycle he used protein and ramified aminoacids. At the end of the cycle he used antiestrogens in order to preserve the testicular production of testosterone.

Case 3

Sociodemographic data and bodybuilding

He was 42 years-old and had started bodybuilding at a non professional levels since he was 25. He worked as a trainer in a fitness centre

AS knowledge

According to the subject, AS were substances responsible for psychological addition since they allowed to go beyond normal physical limits. He started to talk about AS with some

friends and then with some who were recognized among his bodybuilders community to be "AS-experts". He admitted that at the beginning he thought that AS were not responsible for the neoplastic transformation of a cell but were only able to increase the growing speed, then after years of AS use he had broadened the awareness about other potential adverse events (i.e. cardiovascular disease and renal or liver problems).

AS use

He used AS 20 years ago for a couple of year in order to achieve his ideal of physical image and due to the desire to be a part of a group of persons aiming to reach the same body appearance. Initially he used nandrolone, stanozolol, testosterone and GH, with a cyclical pattern following the indications of some friends and then of "AS-experts". He reported some injuries occurred to shoulders and pectoral muscles but he did not put them in relation with AS use.

DS and other drug use

He reported aminoacids and proteins intake. Estrogens were used at the end of AS cycle

Case 4

Sociodemographic data and bodybuilding

He was 41 years-old and started bodybuilding since he was 23, participated to several completion and worked as a personal trainer.

AS knowledge

The subject simply defined AS as "drugs". He reported that AS was a quite usual topic among his bodybuilding mates. According to him AS presented several benefits while adverse events (i.e. gynaecomastia, hepatotoxicity) could be avoided using them with a "scientific criterion".

AS use

He had used AS from the age of 23 to 35 in order to be ready for the competitions. Under the supervision of an "AS-trainer" he used testosterone, GH, insulin. According to him, he obtained only benefits (improvement of physical performance and of muscular mass) since he used AS with a "scientific criterion".

DS or other drugs use

He used a wide range of DS: proteins, aminoacids, creatine, vitamin complex. Every cycle of AS was followed by gonadotropins and estrogens in order to restore the endogenous androgen production and to avoid gynaecomastia.

Case 5

Sociodemographic data and bodybuilding

He was 47, started bodybuilding since he was 25 and sporadically had participated in the past to competitions. He worked as a personal trainer.

AS knowledge

He defined AS as hormones that can be used by ingestion or by injection, that are able to increase androgens (responsible for muscular mass growth) as well as estrogens levels. His source of information were gym mates who were using AS.

He was aware that AS use is related to the danger of cancer and cardiovascular problems. Since he knew their risks he said to have discouraged AS use by the athletes he followed.

AS use

He used AS for a few months (two cycles of AS) at the age of 35 under the supervision of an "AS-expert" in order to further improve his body image. He used testosterone, nandrolone and stanozolol for a 8 weeks cycle. He noticed an increase of physical and psychological power and in sexual desire and did not report any problem related to AS use.

DS or other drugs use

He had used DS at the end of the AS cycle "in order not to overcharge the liver".

Case 6

Sociodemographic data and bodybuilding

He was 25 years-old and practiced bodybuilding for 5 years at non professional level.

AS knowledge

He defined AS as hormones able to increase the muscular mass and widely used internet as a source of information. He reported to be aware of the risks related to AS use but did not go into details.

AS use

He started AS use 6 months ago since he was dissatisfied with his body image. He self-prescribed 8/12 weeks-cycles of androgenic anabolic steroids (testosterone, nandrolone and stanozolol), but wished to be followed by an "expert"/"AS-trainer." At the end of the cycle he used gonadotropins in order to restore the endogenous androgens synthesis. He observed considerable benefits such as an increase in physical performance and in sexual desire. He reported only an inflammation within the site of injection and, sometimes, a sudden change of mood and aggressiveness.

DS or other drugs use

He reported DS intake, but did not go into details. He used antiestrogens, antiandrogens and betablockers in order to avoid AS adverse reactions.

Case 7

Sociodemographic data and bodybuilding

He was 35 years-old and started bodybuilding since he was 17. He was a trainer for professional and non professional bodybuilders.

AS knowledge

AS was defined as an "ergogenic" aid to improve muscular mass. His first source of information was a mate who practiced bodybuilding at professional level. According to the subject, if used with appropriate schedule, AS use was beneficial. Liver and toxicity, cardiovascular problems, sterility were mentioned as potential AS adverse effects.

AS use

He had used cycles of androgenic anabolic steroids (nandrolone, stanozolol, boldenone, mesterolone) in the past in order to obtain results that were better than the simple training. He was initially supervised by some mates and then he started to look for information by himself through internet and books. He was satisfied from the use and did not observe any adverse reaction both in himself and on athletes he trained.

DS or other drugs use

He used progesterone and gonadotropins to restore spermatogenesis at the end of AS cycle. He reported the use of proteins.

Discussion

DS use and knowledge

In our sample population of generic visitors of fitness centres the high prevalence of DS use (84%), principally represented by creatine and proteins/aminoacids, was similar to the few data available in literature (41-85%), strengthening the fact that even recreational athletes often try to push the limits of their sport performance (Oliver 2011; Tsitsimpikou 2011; Cholpicka 2007; Morrison 2004; Mason 2001).

DS use may differ between sporting cultures (Cholpicka 2007) and, as expected, a significantly higher prevalence was observed among bodybuilders while, no association was observed between individual characteristics and attitudes towards DS, or DS use, perception

and knowledge. These data are consistent with the findings coming from direct interviews to bodybuilders using AS, in which all the subjects reported use of DS, especially proteins and aminoacids.

DS intake, however, usually occurred acritically, without a full understanding of the potential benefits and risks associated, often due to a superficial knowledge, as observed in our sample where a satisfactory definition of DS was provided in just a few cases.

Fitness centres *per se* often promote the use of DS through "corners" dedicated to information and sell. According to our results, the trainer was the main advisor for DS, while only a few respondents asked for the advice of qualified personnel, such as doctors or pharmacists. This finding is in agreement with published literature (Molinero 2009; Cholpicka 2007), and it is of some concern, since trainers in fitness centres are not required to have specific background in nutritional sciences to counsel athletes about actual effectiveness safety and legality of DS use.

DS expected benefits and risks

Expected benefits, mainly represented by a quicker recovery and an increased muscular mass/strength (in particular among bodybuilders), were satisfied in a large majority of the surveyed subjects. This finding is the likely result of the intense marketing campaigns of several DS, since very few studies have actually examined the performance advantages (Guyda, 2005). Indeed, the promotion of many DS is often based only on hypothetical benefits coming from animal models, while evidence of advantages in humans is scarce and contrasting (Guyda, 2005; Telford, 1992) and only a few studies have explored benefits and safety data about the long-term use of DS (Schwenk, 2002; Tokish 2004; Philbin 2006). For instance, aminoacid supplementation has not been demonstrated to increase strength as well as endurance and appears unnecessary if one considers that in the typical athlete's diet the protein balance meets the increased sport requirements (Jenkinson, 2008). Moreover, aminoacids may cause gastrointestinal adverse effects such as diarrhea and gastralgia (Jenkinson, 2008). As concerns creatine**,** another quite popular DS, scientific data concerning improvement of sport performance are contrasting (Jenkinson 2008; Mason 2001). Indeed, creatine intake may be detrimental due to the increase in body mass mainly related to water retention (Jenkinson, 2008; Williams, 1998). Although creatine supplementation does not seem to be associated to short-term health risks, long-term risks have not yet been assessed (Mason 2001). Moreover, cases of renal failure related to the association of several DS including creatine have been reported in literature (Thorsteinsdottir, 2006).

Besides contrasting evidence for benefits, the consumption of DS to enhance sports performance or to improve body appearance may, in itself, represent the first step to illegal preparations (Leifman 2011; Suzic Lazic 2011; Dascombe 2010; Wiefferink 2008; Papadopoulos 2006) since it may be associated with risky behaviours such as inappropriate use of medication, excessive intake of energy drinks, or illicit performance-enhancing drugs such as AS (Leifman 2011; Goyda, 2005). This possibility seems indirectly confirmed by our observation concerning the more intense use of DS in bodybuilders, who also admitted to have considered the possibility to use AS.

In our sample 10% of DS source of supply occurred through internet. The raising market has opened up avenues for counterfeiting, therefore, these products are not necessarily produced in accordance with Good Manufacturing Practice. As a consequence, DS may contain unlabelled contaminants or illegal substances (Geyer 2008; de Hon 2007; Van Thuyne 2006; Pipe 2002) and the risk is consistently high for products with lack of controls such as coming from non institutional channels such as the internet sales (Fouillot 2004). Moreover, websites selling DS very often also sell AS and other illegal preparations, provide misleading information and are sources of deceiving practices (Cordaro et al., 2011).

AS knowledge and attitudes

Though the majority of bodybuilders who filled the anonymous questionnaire declared at least a secondary level education, collected data suggest only a limited knowledge about AS as concerns, for instance, the capacity to give a definition of AS or to name AS. Indeed, several non-AS were included among AS list, such as DS (proteins and creatine) commonly used by bodybuilders as well as drugs (cortisone and EPO), which may be used as doping agents, and cocaine. Noteworthy, available studies indicate that AS use is associated with other illicit drug use such as cocaine (Ip 2011; Simon 2006, Striegel 2006).

AS users also exhibited a quite superficial knowledge of AS, with a specific interest in anabolic androgenic steroids as can be noticed in their answers.

Not surprisingly, these substances were not only the best known AS but also the most commonly used by the interviewed bodybuilders. Indeed , in parallel to DS, AS use, anabolic androgenic steroids especially, has consistently raised among non-competitive sports over the last decade, spreading in particular among bodybuilding (Melnik 2009; Mattila 2010; Guyda 2005; Striegel 2006; Wieffrink, 2008 Leifman 2011; Agullò-Calatayud 2008; Simon 2006; Kanayama 2001; Korkia, 1996). According to several studies, the use of AS mainly occurs in males, is directly related to the degree of physical fitness (training years and frequencies) and

is higher in bodybuilders than in other fitness sports athletes especially, if they are preparing for a competition (Striegel 2006). In particular, the explicit use of anabolic androgenic steroids in fitness centres has been reported to be around 10% (Bojsen-Møller 2010).

In agreement with published literature, in our subjects anabolic androgenic steroids represent the most widely used drugs by bodybuilders; steroid regimens usually include a mean of 3-4 agents (both oral and injected drugs), usually taken in doses 5 to 30 times greater than the recommended therapeutic dose and involved cycles ranging 4 to 8 weeks followed by a withdrawal period (from 4 weeks to months) aimed at reducing the risk of adverse reactions (Kicman, 2008; Tahtamouni 2008; Perry 2005). As happened in our study, usually anabolic androgenic steroids are used in association with other AS such as peptide hormones (Ip 2011; Tahtamouni 2008; Striegel 2006; Perry 2005). Antiestrogens and gonadotropins are used in order to restore endogenous testosterone synthesis during these stops (Striegel 2006; Perry 2005).

Reason for AS use and perception of risks and benefits

In agreement with the opinion gathered through the questionnaire and to literature data, all the AS users interviewed declared the central importance of the muscular body appearance (with both aesthetic and sport performance) (Melnik 2009; Striegel 2006; Cafri 2006).

The dissatisfaction with one's aspects as compared to the ideal standard flaunted by the media represents one of the main reason for starting bodybuilding and the consequent AS use (Cordaro 2011; Iriart 2009; Wieffrink 2008; Cafri 2005; Yesalis 2001; Brower 1994). In general, bodybuilders who are more dissatisfied with their body, are more prone to use AS (Goldfield 2009; Schwerin 1997). In our sample, even though the first group of bodybuilders denied the use of AS, some of them admitted to have considered it, suggesting the high pressure for promotion of these substances within bodybuilding world. One bodybuilder admitted during the interview that the dissatisfaction with his body image together with the desire to improve the self-image by increasing muscle mass drove him to AS use.

Almost all the bodybuilders declared to be highly satisfied and to have achieved the expected benefits (such as higher physical performance and a considerable improvement in body image) after starting AS.

A certain tendency to attribute several advantages to the AS use minimizing the potential risks has been observed in the present study. Questionnaire data revealed that only half of potential adverse reaction to AS were detected from a list (table III) and were most frequently

represented by sexual (testicular atrophy, 80.6% and erectile dysfunction, 77.4%), cardiovascular (74.2%) or liver (71.0%) problems.

Indeed, the knowledge of potential adverse reactions were quite limited especially as regards cardiovascular and sexual problems. An alarming picture of underestimation clearly emerged among AS users since only two of them declared to have experienced adverse reactions, referred as mild and reversible in both cases. Moreover, another one user didn't put in relationship a pectoral-shoulder injuries to AS use. In literature, the most commonly reported adverse effects due to the abuse of AS include impotence, acne, liver failure, myocardial infarction as well as psychiatric consequences (Kicman 2008; Casavant 2007; Brower 1994). However other adverse effects may be insidious psyco-physical adverse consequences of AS use may become evident with a considerable delay after long-term use of supraphysiologic doses and the subjects themselves may be unaware of such as damages to the cardiovascular system and, therefore, they may minimize the risks and there's and intrinsic difficulty in collecting adverse effects of what is an underground activity (Kanayama 2008; Kicman 2008). Acne, reported by one of the AS users, according to literature, appears to occur in about 50% of anabolic androgenic steroids users and may represent, therefore, an indirect marker of abuse (Melnik 2007; Voelcker 2010). Questions concerning drug use were intended to detect potential adverse drug reactions due to AS which had required a pharmacological treatment. The use of antibiotic cream for acne may represent a clue of anabolic androgenic steroids use (Voelcker 2010). However, in our sample of bodybuilders, antibiotics were used in 3 cases but were represented by oral formulation.

Moreover, as aforementioned for DS, counterfeit and poorly controlled products is a consistent risk for AS use since their source of supply is usually represented by the black market and internet (Cordaro 2011; Graham 2009).

Source of information for AS

In accordance to what observed in literature (Striegel 2006), source of information for AS principally reported were training colleagues, trainer and the gathering of pertinent literature (books, internet). The lower awareness of risks may be a direct reflection of the primary advisors' knowledge of side effects. These data underline that the source of information may be poor qualified and even partial such as in the case of trainer who may be a user himself and may, therefore, suggest the AS use promoting the benefits and minimizing the risks, as implicitly admitted one of the trainer interviewed. Moreover, specialized internet forums may supply a large amount of information concerning the illicit use of AS in recreational athletes

enhancing the advantages (body image, muscular power) and minimizing or omitting the potential risks (Cordaro 2011).

Concluding remarks

One of the limit of a survey of this nature is the risk of under-reporting. However, it has been demonstrated that information gathered through anonymous self-administrated questionnaire may be reliable (Laure 2007; Stone 2005). Moreover, in our present surveys the numbers were relatively small. This limitation however did not prevent from finding some significant correlations, moreover in particular direct interviews to bodybuilders who admitted AAS use provided relevant information about knowledge and attitudes in this high-risk population. We are now planning to increase the surveyed population and to investigate the possible relationship between AS and DS use and use of other illicit performance-enhancing agents.

In conclusion, our findings highlighted that DS are quite popular among non-professional athletes, and especially in bodybuilders, since they are perceived as useful and harmless. General practitioners/caring doctors should be aware of DS intake, in order to ensure their proper use. In addition, trainers should acquire specific knowledge and education about the topic, as they appear to be the main advisors regarding the use of DS in gymnasiums. Due to the superficial knowledge concerning AS and the underestimations of their adverse reaction together with the higher prevalence than in the general population, fitness centres visitors, and bodybuilders especially, represent an appropriate target for informative interventions.

Tables

Table I. Characteristics of the sample population included in study 1.

	Total	**Males**	**Females**
Number of subjects[b]	50 (100)	47 (94.0)	3 (6.0)
Age (years)[a]	29.5±6.5 (18-44)	29.9± 6.7 (21-44)	22.7±7.2 (18-31)
BMI (kg/m^2)[a]	24±2.1 (19.7-30.1)	24.0±2.1 (19.7-30.1)	23.9±2.1 (20.1-22.3)
Education[b]			
Primary school	3 (6.0)	3 (6.0)	0 (0.0)
Secondary school	35 (70.0)	33 (66.0)	2 (4.0)
Bachelor	11 (22.0)	10 (20.0)	1 (2.0)
Other	1 (2.0)	1 (2.0)	0 (0.0)

Notes: a, mean±SD (range); b, n (%).

Table II. Characteristics of the sample population included in study 2.

	Total	Males	Females
Age [a]	31.2±7.7 (20-49)	31.6±7.6 (20-49)	29.2±12.0 (20-49)
Bodybuilding			
Hours/week [a]	5.7±3.8 (3-25)	5.8±4.1 (3-25)	5.2±1.3 (3-6)
Years started [a]	5.8±5.2 (0.5-20)	6.0±4.6 (0.5-17)	5.0±8.4 (0.5-20)
Total [b]	31 (100)	26 (83.9)	5 (16.1)
Other sports			
Subjects [b]	10 (32.3)	9 (29.0)	1 (3.2)
Number of other sports [a]	1.9±1.3 (1-5)	2.0±1.3 (1-5)	1
Education [b]			
Primary school	7 (22.6)	6 (23.1)	1 (20.0)
Secondary school	17 (54.8)	13 (50.0)	4 (80.0)
Bachelor	6 (19.4)	6 (23.1)	0 (0)
"Other"	1 (3.2)	1 (3.8)	0 (0)
Total	31 (100)	26 (100)	5 (100)

Notes: a, mean±SD (range); b, n (%).

Table III. Recognized adverse reactions due to AS use

	N	%
Testicular atrophy	25	80.6
Erectile dysfunction	24	77.4
Myocardial ischaemia	23	74.2
Liver cancer	22	71.0
Hepatotoxicity	17	54.8
Aggressiveness	17	54.8
Voice deepening	17	54.8
Hirsutism	15	48.4
Clitoral hypertrophy	15	48.4
Depression	14	45.2
Thrombosis	12	38.7
Prostatic hypertrophy	11	35.5
Menstrual disorders	11	35.5
Stroke	11	35.5
Psychosis	10	32.3
Tendon frailty	9	29.0
Acne	8	25.8
Dyslipidaemia	8	25.8
Hypertension	7	22.6
Gynaecomastia	5	16.1
Growth deficit	4	12.9

Table IV. Anabolic substances used by interviewed bodybuilder

Anabolic substances	N	%AS	%users
Anabolic androgenic steroids	*26*	*86,7*	*100*
Nandrolone	6	20,0	85,7
Testosterone	5	16,7	71,4
Stanozolol	5	16,7	71,4
Boldenone	2	6,7	28,6
Trenbolone	5	16,7	71,4
Drostanolone	1	3,3	14,3
Metenolone	1	3,3	14,3
Mesterolone	1	3,3	14,3
Other anabolic substances	*4*	*13,3*	*42,9*
Insulin	2	6,7	28,6
Clenbuterol	1	3,3	14,3
GH	1	3,3	14,3
Total	**30**	**100**	**100**

Herbal remedies use

The use of HR appears to be widely used in industrialized world for several complains. HR are usually considered a safer alternative to conventional treatments, since they are perceived as “natural” and, therefore, beneficial or at least presumed to be free of risks. However, efficacy and safety of many of these products have not been clearly demonstrated. Recently, issues of contamination, adulteration and inappropriate labelling have raised (Mentha 2008).

I have performed a review of the published literature concerning the use of Herbal remedies in the industrialized world, published in chapter 24 (“Herbal Medicines: Epidemiology of their Utilization—A Perspective on the Industrialized World”) of “Herbal Medicines: Development and Validation of Plant-derived Medicines for Human Health”, CRC Press.

The use of HR is common among subjects suffering from chronic conditions due to unmet needs, a “grey area” that conventional prescribed therapy is not able to cover. Most patients do not discuss the use of HR with their health care provider, raising the risk of interactions with concomitant prescribed therapy. The risk is potentially high since up to 60% of herbal users are also under conventional treatment (Al-Windi 2004). Indeed, the number of reports concerning herbal-drug interactions as well as adverse effects are growing (Kennedy 2010).

In “Use of herbal remedies among patients with multiple sclerosis: a nation-wide survey in Italy” I have investigated prevalence, knowledge and attitudes towards HR among multiple sclerosis patients.

Use of herbal remedies among patients with multiple sclerosis: a nation-wide survey in Italy

Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system, with a prevalence about twice in women, and is the leading non-traumatic cause of disability in young adults in the Western World (Alonso et al., 2008; Pugliatti et al., 2006). The impact on patient's quality of life is often significant and the social costs of MS are consistent because of the long duration and the peak in the prime of life, when families and careers are developing (Kobelt et al., 2006; Amato et al., 2002). Recent progress in the treatment of MS is remarkable, however, although new disease modifying agents may reduce the frequency of exacerbations and progression of disability, numerous unmet needs remains to be addressed such as efficacy (impaired effectiveness due to neutralizing antibodies, lack of therapeutic strategies options for progressive MS, etc.), safety (i.e. risks for malignancy and opportunistic infections) and adherence (approved treatments for MS are all parenteral) problems (Kieseier et al., 2009). Psychological problems/affective disorders (especially depression and anxiety), common in MS patients, represents other consistent unmet needs, since they require early diagnosis and appropriate interventions, not always provided (Gay et al., 2010). MS still results for most of patients in different degrees of disabilities requiring medical and non medical interventions. Thus, the burden of symptoms and distress often induce MS patients to seek for herbal remedies and, more extensively, for complementary and alternative medicines (CAM).

The traditional knowledge of herbal remedies and their therapeutic applications, result of thousand years of experience, has been modernized in developed nations, evolving in the so-called "Neo-Western herbalism" (Elvin-Lewis, 2001). Intercontinental travel, immigration and cross-cultural exchange, in general, have broadened the frame of reference of Western herbal medicine introducing the healing practices of other cultures. Echinacea, one of the mainly used plants, may be an example, since it originally came from North America. Herbals remedies are now widely available from many sources including health food stores, supermarkets, direct marketing, natural therapy clinics and pharmacies.

Besides the purpose to promote general health/well being or for disease prevention (Singh et al., 2006), herbal remedies are also used in the treatment of several mild conditions (such as common colds, musculoskeletal problems, gastrointestinal symptoms, etc.) as well as

adjuvant in the management of chronic illness (cancer, cardiovascular diseases, etc.), where conventional treatment are often unfulfilling (Gardiner et al. 2007; Bardia et al. 2007).

The use of herbal remedies have considerably risen since over the last decades in developed countries (Bardia et al. 2007), however, the actual prevalence remains undetermined due to the reduced number of epidemiologic studies. In particular, prevalence data (9-27%) among MS patients derive essentially from surveys dealing with a more extensive picture of CAM (Apel et al., 2006; Nayak et al., 2003; Apel et al., 2005; Leong et al., 2009; Marrie et al., 2003; Olsen 2009; Yadav et al., 2006). Moreover, the rate of disclosure to the caring physicians is often low. Therefore, the use of herbals, so far scarcely investigate among MS, poses several challenges such as interference with conventional drugs as well as tolerability issues.

In the current study we explored prevalence, knowledge and attitudes (why they are chosen, with which purpose, how effective are perceived by users, etc.) towards herbal remedies. In addition, we evaluated the clinical as well as socio-demographic factors related to herbal use. Use and attitudes towards CAM have been also investigated.

Methods

Study design

The present study was a nation-wide observational multicentric survey conducted from January'08 to June'09. The study was previously submitted and approved by the Ethics Committees of each centres and an informed consent was obtained by each patient before the inclusion in the study.

Patients and setting

Patients suffering from multiple sclerosis (MS) according to the revised criteria of McDonalds (Polmann et al., 2005) were enrolled in 14 Italian reference centers for MS. MS outpatients consecutively attending a Neurological Clinic, accepting to participate to the interview, were administered a questionnaire which they could either complete in the ambulatory, with the help of a nurse, or take it at home and send it later through a addressed stamped envelope.

Questionnaire

The questionnaire, anonymous with open as well as multiple choices questions, was structured into five section devoted to the collection of the following data:

I. socio-demographic (age, sex, marital status, education, occupation, residence)
II. clinical features (age at the diagnosis, clinical self-reported disability, see below)
III. pharmacological treatment in the last six months (for SM, for adverse reactions due to SM treatment, for other diseases) and rate of satisfaction
IV. use and attitudes towards herbal medicine (use in the last six months or at any time in the past for MS, to treat diseases not related to MS, kind of products used, rate of satisfaction, occurrence of adverse reactions during the use, place of purchase, suggestion, reasons for using herbals and disclosure to the caring physicians about it)
V. use and attitudes towards other complementary and alternative medicine (CAM) (use, kind, purpose, benefits obtained, suggestion and disclosure of the use to the caring physician).

Self-reported clinical status was evaluated through a scale derived from the Kurtzke Expanded Disability Status Scale (Kurtzke, 2008) previously used in another study (Shinto et al., 2005). For this purpose, subjects were asked to choose among six disease severity categories:

1. None/minimal (no or minimal MS-related symptoms, no limitations in walking ability or in daily activities)
2. Mild (noticeable MS-related symptoms, but no limitations in walking or in daily activities)
3. Moderate (many MS-related symptoms that affect daily activities, no support needed to walk 1 block)
4. Some support needed for walking (significant MS-related symptoms that limit physically demanding activities; support needed to walk)
5. Walker/two-handed crutch (significant MS-related symptoms that limit daily activities, walking limitations: only short distances with a walker or two-handed crutches)
6. Unable to walk (severe MS-related symptoms, restricted to a wheelchair or bed).

Though the survey was not focused on the use of Cannabis sativa, a specific question about it was placed at the beginning of section IV, in order to avoid any potential bias in the subsequent answers about phytotherapy.

Two different and complementary typology of questions investigated the use of herbal remedies: an open one allowed the patients to freely name herbal remedies, while a close question was intended to recollect names through a list of medicinal herbs selected among the most popular according literature.

The questionnaire was tested among 68 SM outpatients (72% women, age (mean±SD) of 38.5±11.5 years and suffering from MS since 9.5±6.6 years) consecutively attending the coordinating centre of Gallarate (VA). As a consequence, some changes (inversion in the order of some questions) were carried out to ameliorate the comprehension and compilation of the questionnaire.

Data collection

Between January and June'09 the collected data were inserted into a digital archive (MS excel). Records were validated according to the International Quality Standard ISO 2859 guidelines (ISO 2859-4:2002) and the database was considered suitable for analysis.

Before the analysis each record was checked for intra and inter section coherence. In particular, the reported products (drugs, herbs or other CAM) were carefully identified and, if necessary, reallocated into the appropriate sections. Patients failing to answer the questions about the use of medicines, herbals or CAM, but subsequently reporting the names of a specific product, were considered as users.

To assess any potential difference among geographic areas, Italian region were grouped into five macro-regions according to the National Institute of Statistic (ISTAT) classification (http://www.istat.it/).

Outcome measures

The main outcome measure was the prevalence of patients using herbal products in the previous 6 months. Similarly to other surveys, we chose a six-month interval in order to balance the detection of the widest number of users with the highest reliability in the answers. In addition, we also evaluated the use at any time in the past to gain a more extensive picture of the herbal use.

Statistical analysis

Collected data were analyzed with a commercial software (Stata10, Stata Corp, College Station, TX, USA). Descriptive statistics were used to estimate the prevalence and attitudes towards herbal use. We also used a logistic multivariate analysis to investigate any association between herbal use (in the previous 6 months and at any time in the past) and sociodemographical and clinical factors.

Results

From January'08 to June'09, 2419 questionnaires for MS were collected from 14 Italian Centres. According to the ISTAT macro-regions, 948 (39.2%) of them came from North West, 313 (12.9%) from North East, 70 (2,9%) from Central Italy, 463 (19.1%) from South and 625 (25.8%) from Isles. Socio-demographic and clinical features or the sample surveyed are presented in table 1. Respondents were principally female (68.8%), with a mean age (±SD) of 40.6±10.8 (range: 10-74) years and with a middle-high level of education (i.e. 13 years devoted to study in 1006 cases, 45.7%). Patients were suffering from MS from 8.4±6.6 years (range: 46-0) and in more than one half of cases the disease status was subjectively defined as "None/minimal" (1367 patients, 56.5%).

Herbal use for MS or other diseases

The actual or past use of Cannabis was declared by 280 (11.6%) of the participants; globally, 2297 (95.0%) subjects answered to this question.

The use of herbal remedies to treat MS was declared by 326 subjects (15.0%, 95% confidence interval [CI], 13.5-17.0%) and 134 of them (6.2%, 95% CI, 5.2-7.3%) used herbal remedies within the last 6 months. These products were used as adjuvant to conventional therapy (42.9%), to treat adverse drug reactions (29.8%) or as alternative to drugs (20.2%).

The use of herbal remedies to treat other diseases than MS was declared by 762 patients (48.2%; 95% CI, 45.7-50.7%) and 262 of them (16.6%; 95% CI, 14.8-18.5%) used herbals within the last 6 months. In 226 cases (29% of herbal users) herbs were used to treat 1.7±1.2 (mean±SD, range 1-9) diseases, among which were mentioned: gastrointestinal diseases upper respiratory ways in 131 (17.2%) cases, sleep disturbances in 105 (13.8%), anxiety in 82 (10.8%), genito-urinary infections in 60 (7.9%), migraine in 48 (6.3%), depression in 38 (5.0%), osteoarticular pain in 38 (5.0%), cardiovascular diseases in 34 (4.5%), dermatitis in

34 (4.5%), dysmenorrhea in 31 (4.1%), allergy in 21 (2.8%), ocular inflammations in 17 (3.1%), fever in 10 (1.8%). In 67 cases (8.8%) herbs were used for "other conditions", mainly hydric retention (13, 1.7%) and weight problems (10, 1.3%).

Globally, 862 subjects out of 2419 (35.6%) (38.0% of respondents, 95% CI, 36.0-40.0%) declared to have used in the last six month/any time in the past herbal remedies for MS or other diseases.

CAM use

The current or past recourse to other CAM was declared in 1028 cases (42.5% of sample), and consisted in vitamins/minerals (626, 60.9% of CAM users), other dietary supplements (498, 48.4%), massages (259, 25.2%), homeopathy (200, 19.5%), acupuncture (92, 8.9%), and other CAM (111, 10.8%).

Benefits were perceived by the majority of patients (82.2%, among which 40.1% were totally satisfied while 42.2% were partially satisfied by CAM use). Disclosure to the caring doctor was declared by 677 subjects (65.9% of the users).

Predictors of the use of herbal products in the last 6 months

Table 2 depicts the likelihood of herbal use by individuals' sociodemographic and clinical features according to univariate and multivariate analysis. Women appeared to be more prone to use herbal remedies than men (OR= 1.69). The likelihood to use herbals increased together with the level of education (OR= 1.61 to 2.17). The use appeared to be influenced by the geographic area, being higher in the Northern Italy (OR= 1.50). CAM use as well as the perception of benefits from it, were other important determinants (OR= 3.57 and 6.25, respectively). The multivariate analysis of the use at any time in the past confirmed these results. No clinical features appeared to be related to the use. In addition, dissatisfaction with conventional treatment for diseases other than MS was related with the use of herbal products.

Features of herbal use

Among a total of 765 substances mentioned, 560 (73.2%) were properly herbal remedies. In particular, 385 subjects (44.7% of users) named at least 1 or more herbal products (1.5±0.9 herbs/subject mean±SD; range: 1-5), among which the most popular (in at least 5 users) have been listed in table 2. Propolis (40, 4.2% of users), aloe vera (37, 4.3%), and valerian (31, 3.6%), were the in the lead.

Substances other than herbal remedies, mentioned in 205 (26.8%) cases, were represented by: vitamins/supplements in 83 cases (10.8%), homeopathic remedies in 43 (5.6%), Bach's flowers in 24 (3.1%), conventional drugs in 7 (0.9%), algae in 6 (0.8%), cosmetics in 3 (0.4%), cannabis in 1 (0.1%). In addition Hebener therapy was named in 1 case (0.1%), while in 37 (4.8%) handwriting was illegible.

Specific use of herbs was further explored by a second question in which the patients were invited to select if they had use one of the listed herbs (Table 4). Among the herbs in the list: ginseng (282, 32.7% among users), followed by Hypericum perforatum (122, 21,7%), liquorice (113, 13.1%) and Echinacea (105, 12.2%) were the most frequently selected.

631 (73.2%) subjects were completely (36.2%) or at least partially (37%) satisfied by the use of herbal remedies. Benefits declared were represented by the complete remission of symptoms in 73 cases (8.5% of the users), improvement in 345 (40.0%), reduced intake of conventional drugs in 62 (7.2%) and "other" in 42 cases (4.9%). During the use of herbal products 44 patients (5.1% of the users) denounced the occurrence of new disturbances, among which the most frequent were the worsening of neurologic symptoms in 21 (2.4% of the users), followed by psychological symptoms in 9 (1.0%), gastrointestinal problems in 5 (0.6%), arrhythmias in 3 (0.3%), fever in 2 (0.2%), rash in 1 (0.1%), hypotension in 1 (0.1%), flushing in 1 (0.1%), gastralgia during the use of devil's claw in 1 (0.1%).

Herbal products were purchased at the herbalist's shop in 462 cases (53.6% of the users), pharmacy in 373 (43.3%), supermarket /drugstore in 60 (7.0%). The 39 cases (4.5%) in which the term "other" was indicated are presented in table 4.

Herbal remedies were used upon the advice of herbalist in 276 (32.0%) patients, acquaintances in 223 (25.9%), pharmacist in 134 (15.5%), general practitioner (GP) 131 (15.2%), media in 53 (6.1%), internet in 53 (6.1%), caring neurologist in 24 (2.8%), alternative practitioner in 15 (1.7%), self prescription in 5 (0.6%), other specialist in 5 (0.6%), nutritionist in 4 (0.5%), nurse in 1 (0.1%). 361 users (41.9%) declared to have disclosed the herbal use to GP or to the caring specialist.

The reasons for using herbal products were it was less toxic than conventional treatment for 277 subjects (32.1% of users), it had been recommended for 164 (19.0%) it was effective for 162 (18.8%), the purpose to follow a healthy lifestyle for 146 (16.9%), curiosity for alternative medicine for 126 (14.6%), inefficacy of conventional drugs for 39 (4.5%).

In addition, 470 subjects had used regularly (83, 9.6% of herbal users) or occasionally (377, 43.7%) herbal treatment before the occurrence of MS.

Discussion

Italian MS patients are estimated to be around 57000 (http://www.aism.it). In this study almost 2500 SM patients were surveyed, representing a consistent sample, higher than most of other studies in patients suffering from MS or other chronic diseases. Moreover, the main outcome is devoted specifically to herbal than to CAM use. A herbal use for any purpose in more than one third of the MS patients surveyed denoted it was quite popular. In particular more than 6% and 16% of subjects had used herbal remedies the previous six months for MS or other diseases, respectively. This is in accordance with the prevalence observed among other group of MS patients (9-26%) (Apel et al., 2006; Apel et al., 2005 Nayak et al., 2003). In the latter part of the 20th century herbal medicine use, became a substantial and growing part of health-care behaviour in the industrialized world. The use of CAM, and herbal remedies in particular, seems to be higher among MS patients than in the general population (Olsen, 2009). Indeed, a considerable lower prevalence has been observed among Italian general population. In an Italian nationwide survey (nearly 80 thousands subjects interviewed, with a section reserved for CAM) performed in 1999, herbal users accounted for 5% of participants (Menniti-Ippolito et al. 2002). However, this lower prevalence may be influenced not only by the difference between the general population and MS subjects (chronic ill affected subjects), but also by the structure of that survey itself, which was not specifically devoted to herbal remedies.

Interest in herbal remedies may be due to a dissatisfaction with conventional health care and the perception that those are safer than pharmaceutical drug and may also reflect a desire for a personal control over oneself health to take a more active part in therapy and prevention of illness. In our study, the use herbal remedies was related with the choice to follow a healthy lifestyle, together with dissatisfaction with drug treatment. However, the tendency in our sample was not to give up conventional treatment in lieu of herbal remedies, but to use them as adjuvant to conventional therapy.

Our findings are consistent with those of most studies among general population, since a typical herbal user presents the following features: female (OR 1.69), with a higher level of education (secondary school/university; OR 1.61-2.17), living in the Northern Italy (OR: 1.50), being dissatisfied with the conventional treatment of diseases other than MS (OR: 3.21), using and being satisfied by CAM (3.57 and 6.25, respectively) (Gardiner et al., 2007; Kelly et al., 2006; Wheaton et al., 2005; Al-Windi 2004; MacLennan et al 2002).

Although controversial, Cannabis use appear to be quite popular among subjects suffering from MS, especially to manage MS symptoms such as pain, spasticity, mood, tremors, fatigue or bladder dysfunction (Yaldav et al., 2006). In particular our sample showed a similar prevalence (12 %) to those (14-16%) obtained in other though smaller studies (Clark et al., 2004; Martínez-Rodríguez et al., 2008; Chong et al., 2006).

Our findings were similar to those of other large surveys as concerns the most commonly mentioned herbs (table 1) as well as the most commonly selected (table 2) ones (Gardiner et al., 2007; Singh et al., 2006). According to the US 2002 National Health Interview Survey, the most commonly herbal products used were Echinacea (40%), ginseng (24%), gingko biloba (21%), garlic (20%), St. John's wort (12%), peppermint (12%), ginger supplements (11%), soy supplements (9%), chamomile (9%), kava kava (7%), valerian (6%), saw palmetto (6%) (Gardiner et al., 2007)

Similarly, the most commonly mentioned herbs among Canadian populations were: echinacea (27%), garlic (21%), gingko biloba (11%), herbal tea (6%), St. John's wort (6%), ginseng (5%), flaxseed oil (4%), evening primrose oil (3%), devil's claw (3%). (Singh et al., 2006).

Though small differences concerning the less represented herbs, resemblances largely prevail if the most popular herbs, i.e. echinacea (for cold symptoms and to enhance the immune system), ginko biloba (to improve memory), ginseng (as an energy booster) and garlic (for hypertension and dyslipidaemia) are considered, suggesting a globalisation in herbal market.

Our findings concur with previous studies regarding the disclosure to the health provider who is informed in less than half of cases, with considerable risks of adverse drug reactions an potential interferences with drug therapies.

The knowledge of herbal medicine appears to be often inaccurate since caring physician has been reported to be rarely a source for information and certain degree of confusion in terminology has been observed; vitamins and supplements, homeopathic remedies and Bach's flowers, for instance, were confused with proper herbal remedies.

The level of satisfaction was high (more than 70%), and only in 6% of cases, new disturbances occurred; however they were mainly related to new sensitive symptoms or impairment of MS clinical picture, and only in one case the patient clearly related the disturbance occurred to the herbal remedies (gastralgia after using devil's claw).

Although, some data in literature suggest that CAM may be beneficial in the management of MS symptoms, the actual efficacy and safety of such therapies in MS have not been clearly established because of randomized clinical trials are scant and sample size usually small (Olsen, 2009). Herbal remedies, in particular are usually considered a safer alternative to

conventional treatments, since they are perceived as ‘natural’ and, therefore, beneficial or at least free of risk. Therefore, the use of herbal products is a matter of concern for health care providers since the number of reports concerning herbal-drug interactions as well as adverse effects are growing (Kennedy et al., 2010).

In conclusion, this large observational survey, among more than 4% of Italian SM patients, allowed the creation of the first database containing detailed information about the use of herbal remedies in Italian SM patients. The degree of involvement of the caring physician (source of information, disclosure) in herbal treatment appears to be scarce, with the potential risk of adverse reactions or interference with conventional treatments. The knowledge of socio-demographic or health features potentially related with the use of herbal products is clinically relevant since it may allow physicians to identify the most likely users and, therefore, to direct appropriate educational and other preventive interventions.

Tables

Table 1. Socio demographic and clinical features of the population surveyed

	Overall N (%)	**Median (25-75); range**
Characteristics		
Age		
Years	-	40 (33-48); 10-74
Duration of the disease		
Years	-	7 (3-12); 0-46
Gender		
Male	729 (30.2)	-
Female	1665 (68.8)	-
Missing answer	25 (1.0)	-
Living		
With someone	2157 (89.1)	-
Alone	222 (9.2)	-
Missing answer	40 (1.7)	-
Marital status		
Single	712 (29.4)	-
Married/cohabiting	1481 (61.2)	-
Separated/divorced	175 (7.2)	-
Widowed	33 (1.4)	-
Missing answer	18 (0.8)	-
Education		
5-8 yrs	882 (36.5)	-
13 yrs	1106 (45.7)	-
>13 yrs	383 (15.8)	-
Missing answer	48 (2.0)	-
Occupation		
Yes	1442 (59.6)	-
No	959 (39.6)	-
Missing answer	18 (0.8)	-
Geographic Area		
Northwest	948 (39.2)	-
Northeast	313 (12.9)	-
Centre	70 (2.9)	-
South	463 (19.2)	-
Isles	625 (25.8)	-

Table 2 Univariable and multivariable analysis of the predictors of the use of phytotherapy (part I)

		Univariable		Multivariable
Characteristics	**Herbal use N (%)**	**OR (95% CI)**		**OR (95%CI)**
Age	-			
Per year		0.99 (0.98-1.00)		1.00 (0.98-1.01)
Duration of the disease	-			
Years		1.00 (0.99-1.02)		
Gender				
Male	70 (10.4)	1[Reference]		1[Reference]
Female	257 (16.4)	1.69 (1.28-2.22) ***		1.33 (0.98-1.82)
Living				
With someone	287 (14.0)	1[Reference]		
Alone	35 (17.0)	1.23 (0.85-1.82)		
Marital status				
Single	100 (14.8)	1[Reference]		
Married/cohabiting	201 (14.5)	0.98 (0.76-1.27)		
Separated/divorced	21 (12.9)	0.85 (0.52-1.42)		
Widowed	4 (14.8)	1.00 (0.34-2.67)		
Education				
5-8 yrs	79 (19.3)	1[Reference]		1[Reference]
13 yrs	167 (15.6)	1.61 (1.21-2.14)**		1.24 (0.90-1.71)
>13 yrs	74 (19.9)	2.17 (1.54-3.06)***		1.44 (1.02-2.11)*
Occupation				
Yes	211 (15.2)	1[Reference]		1[Reference]
No	114 (13.2)	1.18 (0.92-1.51)		0.89 (0.66-1.18)
Geographic Area				
Northwest	149 (16.5)	1[Reference]		1[Reference]
Centre	17 (25.8)	1.75 (0.98-3.13)		1.54 (0.98-2.98)
Isles	66 (11.7)	0.67 (0.49-0.91)*		0.66 (0.46-0.94)
Northeast	52 (17.5)	1.07 (0.76-1.52)		0.92 (0.67-1.43)
South	43 (9.9)	0.56 (0.39-0.80)**		0.53(0.36-0.79)**
Geographic Area (grouped)				
Else	126 (11.8)	1[Reference]		
North	201 (16.8)	1.50 (1.18-1.90)**		

OR= Odds ratio; CI= confidence interval 95%;(g)=grouped data; *= P<0.05; **=P<0.01; ***P<0.001

Table 2 Univariable and multivariable analysis of the predictors of the use of phytotherapy (part II)

		Univariable		Multivariable
Characteristics	**Herbal use N (%)**	**OR (95% CI)**		**OR (95%CI)**
Quantiles of years disease				
≤3 yrs	80 (14.0)	1[Reference]		1[Reference]
4-7 yrs	95 (16.5)	1.22 (0.88-1.68)		1.24 (0.88-1.77)
8-12 yrs	71 (14.3)	1.03 (0.73-1.45)		1.08 (0.74-1.58)
>12 yrs	72 (14.8)	1.07 (0.76-1.51)		0.99 (0.67-1.48)
		Univariable		**Multivariable**
Characteristics	**Herbal use N (%)**	**OR (95% CI)**		**OR (95%CI)**
Disease severity (symptoms, limitations in movements)				
None/minimal	186 (14.3)	1[Reference]		
Mild	56 (17.8)	1.30 (0.94-1.81)		
Moderate	37 (14.6)	1.03 (0.70-1.51)		
Support needed for walking	28 (15.5)	1.10 (0.71-1.70)		
Walker/two-handed crutch	6 (8.0)	0.52 (0.22-1.22)		
Unable to walk	8 (13.1)	0.91 (0.42-1.94)		
Disease severity (grouped)				
None/minimal or mild	242 (15.0)	1[Reference]		
Moderate/some support needed	65 (15.0)	1.00 (0.75-1.35)		
Severe (walker, c/unable to walk)	14 (10.3)	0.65 (0.37-1.15)		
Satisfaction for conventional treatment for MS				
A lot	118 (14.1)	1[Reference]		
Somehow	143 (14.3)	1.02 (0.78-1.33)		
Little	28 (15.7)	1.14 (0.73-1.79)		
No	8 (15.7)	1.14 (0.52-2.48)		
No answer	30 (15.2)	1.09 (0.71-1.69)		
Satisfaction for conventional treatment for MS (g)				
A lot/somehow	261 (14.2)	1[Reference]		
Little/no	36 (15.8)	1.12 (0.77-1.65)		
No answer	30 (15.2)	1.08 (0.72-1.63)		
Satisfaction for conventional treatment of side effects				
A lot	34 (16.8)	1[Reference]		1[Reference]
Somehow	68 (18.9)	1.15 (0.73-1.81)		1.05 (0.64-1.75)
Little	15 (22.4)	1.42 (0.72-2.82)		1.12 (0.50-2.50)
No	3 (16.7)	0.98 (0.27-3.60)		1.15 (0.26-5.12)
No answer	207 (12.8)	0.72 (0.49-1.08)*		0.79 (0.51-1.23)

OR= Odds ratio; CI= confidence interval 95%;(g)=grouped data; *= P<0.05; **=P<0.01; ***P<0.001

Table 2 Univariable and multivariable analysis of the predictors of the use of phytotherapy (part III)

		Univariable		Multivariable
Characteristics	**Herbal use N (%)**	**OR (95% CI)**		**OR (95%CI)**
Satisfaction for conventional treatment of side effects (g)				
A lot/somehow	102 (18.2)	1[Reference]		
Little/no	18 (21.2)	1.21 (0.69-2.13)		
No answer	207 (12.8)	0.66 (0.51-0.86)*		
Satisfaction for conventional treatment of diseases other than MS				
A lot	42 (16.3)	1[Reference]		1[Reference]
Somehow	134 (20.4)	1.31 (0.90-1.93)		1.50 (0.98-2.29)
Little	24 (20.9)	1.36 (0.78-2.37)		1.60 (0.85-3.02)
No	5 (38.5)	3.21 (1.0-10.31)*		4.54 (1.18-17.50)*
Satisfaction for conventional treatment of diseases other than MS (g)				
A lot/somehow	176 (19.3)	1[Reference]		
Little/no	29 (22.7)	1.22 (0.79-1.92)		
No answer	122 (10.0)	0.46 (0.36-0.60)***		
Use of alternative medicine				
Yes	243 (24.2)	1[Reference]		
No	61 (8.2)	0.28 (0.21-0.37)***		
No answer	23 (4.5)	0.15 (0.09-0.23)***		
Perception of benefit from CAM use				
Yes	126 (31.7)	1[Reference]		1[Reference]
Partially	95 (22.1)	0.61 (0.45-0.83)**		0.60 (0.43-0.83)**
No	16 (16.0)	0.16 (0.23-0.73)**		0.43 (0.23-0.80)**
No answer	90 (6.7)	0.16 (0.12-0.21)***		018 (0.13-0.25)***

OR= Odds ratio; CI= confidence interval 95%;(g)=grouped data; *= P<0.05; **=P<0.01; ***P<0.001

Table 3. Most popular (≥5 users) herbal products listed

Herbs	N	% Respondents	% Users
Propolis	40	8,1	4,6
aloe vera	37	7,5	4,3
Valerian	31	6,3	3,6
Ribes nigrum	18	3,6	2,1
“Infusion” (NS)	18	3,6	2,1
Arnica	15	3,0	1,7
Echinacea	14	2,8	1,6
“10 erbe”	13	2,6	1,5
Ginseng	11	2,2	1,3
Blueberry	11	2,2	1,3
Uva ursi	11	2,2	1,3
Calendula	8	1,6	0,9
Hypericum perforatum	7	1,4	0,8
papaya	7	1,4	0,8
Ginkgobiloba	6	1,2	0,7
“Herbalife”	6	1,2	0,7
“PC 28”	6	1,2	0,7
Devil's claw	5	1,0	0,6
Chamomile	5	1,0	0,6
Liquorice	5	1,0	0,6
“Sollievo”	5	1,0	0,6
Laxative infusion	5	1,0	0,6
Veravis	5	1,0	0,6

“10 erbe”, “PC28”, “Sollievo” and “Veravis”: dietary supplements containing multiple herbal components; NS= not specified

Table 4. Selection of herbs among the list of commonly used in literature

Herbs	N	% Respondents	% Users
Ginseng	282	50,1	32,7
Hypericum perforatum	122	21,7	14,2
Liquorice	113	20,1	13,1
Echinacea	105	18,7	12,2
Gingko Biloba	85	15,1	9,9
Garlic	30	5,3	3,5
Enotera	22	3,9	2,6
Kawa kawa	8	1,4	0,9
Arecha catechu	1	0,2	0,1
Other	158	28,1	18,3

Table 5. Place of purchase of herbal remedies

	N	% Respondents	% Users
Herbalist's shop	462	60,6	53,6
Pharmacy	373	48,9	43,3
Supermarket/drugstore	60	7,9	7,0
Other	39	5,1	4,5
Direct producer	*12*	*1,6*	1,4
Home growing	*5*	*0,7*	0,6
Friends	*3*	*0,4*	0,3
Parapharmacy	*3*	*0,4*	0,3
Physician	*2*	*0,3*	0,2
At home	*2*	*0,3*	0,2
Naturopath	*2*	*0,3*	0,3
smart shop	*1*	*0,1*	0,1
Whenerver it happens	*1*	*0,1*	0,1
Bar	*1*	*0,1*	0,1
WEB	*1*	*0,1*	0,1
By mail	*1*	*0,1*	0,1
Missing answer	*8*	*1,0*	0,9
Missing answer	99		11,5

Conclusions

Pharmacoutilization studies allow to obtain a picture of medication pattern as well as DS/HR and other substances such as doping agent use within a selected population.

I have observed that polypharmacy was quite common in outpatients attending a dental clinic and an increasing risk of DDI with age and drug used. These findings underline the crucial importance of a preoperative assessment including a complete evaluation, documenting all the medications as well as DS and HR within the dental record.

Medication profiles and potential DDI knowledge is essential for safe practice in dentistry and also represents an important base for planning undergraduate as well as postgraduate teaching in clinical pharmacology.

The results from élite cyclers confirmed the widespread use of DS despite the lack of evidence about their efficacy and the potential risks. Moreover, I have noticed a superficial and "hematic-oriented" doping together with a potential hidden use, suggested by "denial policy".

As a whole, I have observed a widespread interest in DS and AS by fitness centre visitors and, in particular, among bodybuilders, as well as a very limited and selective perception of related risks.

The results of the present studies, therefore, provide the basis for direct interventions aimed at increasing the knowledge and awareness of the risks in doping in both élite and recreational sports through educational and preventive programs. These measures aimed at reducing the improper use of substances in recreational athletes appears to be of critical importance at the individual as well as at the societal level.

Therefore, physician should not only be an active part in the promotion of sport and exercise, but also be aware of DS and other performing-enhancing drug use.

Trainers, who represent one of the main advisors should acquire specific knowledge about the about actual effectiveness, safety and legality of DS use.

In the survey among MS patients, HR use appeared to be quite common, with the attempt to follow a healthy lifestyle, together with dissatisfaction with conventional drug treatment. However, the tendency in our sample was not to give up conventional treatment in lieu of herbal remedies, but to use them as adjuvant.

Features associated with HR use in our sample were represented by: female, with a higher level of education, living in the, being dissatisfied with the conventional treatment of diseases other than MS, using and being satisfied by complementary and alternative medicine .

The degree of involvement of the caring physician (source of information, disclosure) in herbal treatment appears to be scarce, with considerable risks of adverse drug reactions an potential interferences with drug therapies.

In conclusion, pharmacoutilization survey represent a suitable tool to gather information about use, knowledge and attitudes towards drugs and other substances such as DS/HR, doping or other illicit agents. Collected data may help to find out potential predictors associated with the use of these substances and, therefore, to identify subjects who may benefit by an educational intervention.

Pharmacovigilance

During my PhD study programme I have also followed other pharmacoepidemiologic topics dealing with pharmacovigilance a discipline focused on monitoring the safety profile in the real life setting. Indeed, pre-marketing clinical trials usually involve a relatively small and usually selected (age, sex, absence of other comorbidity, etc…) number of patients for a relatively short period of time. However, once marketed, drugs will not be used under the same conditions and may be used by millions of patients, across a wide range of age groups, who may also be affected by other comorbidity and may be taking other medications. Though clinical trials are usually able to detect the more common and predictable adverse drug reactions (ADR), rarer ADR may only be highlighted once the drug is used by a large number of patients under the conditions of everyday use.

The case report represents the basilar and simplest approach to pharmacovigilance, however, it is not a suitable tool in case of rare (<1/100'000) ADR However, due to their low frequency and difficult differential diagnosis, they are hardly detected through spontaneous reporting systems. Case-control studies are suitable tools to identify such rare and often life-threatening ADR, however they require collaborative network able to afford adequate quantity/quality of data.

Hereafter will follow the abstract list of case report/case series of unusual ADR presented at national and international meetings. The ADR has been evaluated by in the light of the available literature and according to OMS causality assessment criteria

- **Finasteride-Associated Central Serious Chorioretinopathy,** *8th ISOP Annual Meeting, Buenos Aires, 2008; Drug Safety 2008; 31 (10): 885-960*

- **Bisphosphonate-Related Osteonecrosis of the Jaw: Description of Six Cases**, *9th ISOP Annual Meedting, Reims, 2009*; *Drug Saf 2009;32(10*

- **Collaborative Hospital-Based Surveillance Network of Drug-Induced Pancreatitis: A Feasibility Study in Italy**, *8th ISOP Annual Meeting, Buenos Aires, 2008, 34° Congresso Nazionale SIF, Rimini, 2009, Drug Safety 2008; 31 (10): 885-960.* This study was realized by a grant of Ministry of Health for pharmacovigilance activities (DGR VII/8501 del 22.03.02)

- Hepatotoxicity after high-dose methylprednisolone for demyelinating disease.

This case report has been presented at 7th ISOP Annual Meeting, Bornemouthm, UK, 2007 and published in extenso in Clin Neuropharmacol. 2010 Jan-Feb;33(1):52-4.

Abstract

Liver toxicity, although not mentioned among the possible adverse effects of corticosteroids, has been occasionally reported in literature. We observed 2 cases of hepatotoxicity after a high-dose methylprednisolone treatment of a demyelinating disease and evaluated the potential relationship in the light of available evidence. The first patient developed a histologically documented acute hepatitis and recovered after 3 weeks. In the second patient, a mild augmentation of liver enzymes occurred, followed by normalization in a few days. The causal relationship between hepatotoxicity and methylprednisolone treatment was deemed probable in both cases. Careful review of the literature suggests that corticosteroid-induced liver damage may be more frequent than commonly believed.

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