1 g/day was used for 4 days, but she felt worse and re-admitted in third day. She had jaundiced scleras and hepatomegaly (HM) (3 cm). ALT was 977 U/L, AST 1288 U/L, t. bilirubin 32 mg/dL (d. 19), ALP 1062 U/L (64–306), HBsAg, anti-HBc IgM, anti-HCV, ASMA, and IgM Ab. against HAV, EBV-VCA, CMV, and HSV were (-). MR cholangiography was normal. Biopsy: prominent cholestasis, acute cholangitis, moderate fibrosis. Ornidazole was discontinued and in one month, laboratory returned to normal. During one year, she is doing well.

**Case 2:** A 50-year-old woman presented with jaundice, dark urine and weakness of 7 days. 3 weeks ago, she was prescribed ornidazole (1 g/day for 3 days) for vaginitis and used for 3 days. 4 days after discontinuation, the symptoms began. She reported an acute hepatitis after ornidazole use of 7 days 10 years ago. She had jaundiced skin and scleras and HM (2 cm). ALT was 3042 U/L, AST 1665 U/L, t. bilirubin 47.9 mg/dL (d. 19.3), AP 422 U/L, HBsAg, anti-HBc IgM, anti-HAV IgM, anti-HCV, HCV-RNA, anti-HEV, anti-LKM, ASMA, FANA, and IgM Ab. against CMV and EBV VCA were (-). An abdominal USG was normal. Liver biopsy: focal and bridging necrosis. 52 days after laboratory returned to normal. For 8 months, she is healthy.

**Case 3:** A 25-year-old woman was initiated ornidazole (1 g/day) for vaginitis. 3 days later, readmitted with nausea and the drug was discontinued. 15 days later, she presented with jaundice, dark urine, and vomiting. She had jaundiced scleras. ALT was 1160 U/L, AST 790 U/L, t. bilirubin 10.1 mg/dL (d. 8.7), AP 431 U/L. Anti-HAV IgM, HBsAg, anti-HBc IgM, Anti-HCV, HCV RNA, anti-HEV, and IgM Ab. against CMV and EBV-VCA were (-). MR cholangiography was normal. Biopsy: prominent cholestasis, acute cholangitis, moderate fibrosis. Laboratory returned to normal in one month. For one year, she is doing well.

Ornidazole is commonly used and may lead to hepatic toxicity. Cholestasis, cholangitis, fibrosis or necrosis may be seen. Clinicians should be aware of the hepatotoxicity of this drug.

### P073. Adverse events associated with the single use of drugs during Biodisponibility studies

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**Aim of the study:** The purpose of this study was to quantify the adverse events produced by the single administration of drugs during bioavailability studies that were made in two years. Drugs used had a half-live between 4 to 10 hours.

**Methods:** An observational longitudinal and retrospective study was made using the data of 264 healthy volunteers, 132 male and 132 female, that were included in 11 studies of bioavailability using several drugs. In each one of these studies 24 volunteers were included, 12 male and 12 female. Adverse events were evaluated and quantified.

**Results:** Of the 264 volunteers, 66 (25%) presented adverse events in a total of 91, being more common in women (68.2%) than in men. Severity of the adverse events was mainly quantified as light in 72.6% and 27.4% were agruped as moderated. Causality was found in 95% of all cases, which were qualified as adverse effects. Most common adverse effects were related with digestive system (59.3%). Average of adverse events per biodisponibility study was of 6.6.

**Conclusions:** Average and type of adverse effects found corresponds to those reported in the literature for each drug tested, therefore results of this study are representative of adverse events observed in an open population after a single dose administration, and this is what could be expected to obtain in Mexico, if a proper program of pharmacovigilance existed.

### P074. Hyperpigmentation associated with the use of serotonin reuptake inhibitors

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**Introduction:** Till November 2001 the Netherlands Pharmacovigilance Centre received a total number of 1,602 reports concerning suspected adverse drug reactions (ADRs), associated with the use of serotonin re-uptake inhibitors (SSRIs). Seven reports mentioned the occurrence of hyperpigmentation associated with this class of drugs. This possible ADR is not mentioned in the Dutch Summary op Product Characteristics texts of citalopram, fluoxetine, sertraline and venlafaxine. Skin reactions to SSRIs have been reported in literature and mainly involve rash. To our knowledge hyperpigmentation of the skin has not been described previously.

**Aim of the study:** Description of reports referring to the association between the use of SSRIs and hyperpigmentation of the skin.

**Methods:** Case series based on data originating from the Netherlands Pharmacovigilance Centre Lareb.

**Results:** A total number of seven reports, concerning one man and six women, have been submitted to the Netherlands Pharmacoviglance Center. Three reports mentioned the use of fluvoxamine as suspected medication, two reports paroxetine, one report sertraline and finally one report citalopram. The time of onset varied between a couple of days and four months. An altered facial pigmentation, which sometimes impresses as chloasma, was reported four times. In three reports the exact localisation of pigmentation is not known. It is striking that all seven cases have been reported during spring or summer.

The type of changes in the colour of the skin are suggestive for a disturbance of the melanin pigmentation itself. Hyperpigmentation may be caused by an increase of

$\alpha$-MSH. This hormone is formed out of the pro-hormone POMC, which is being controlled by dopamine and serotonin. The exact role of serotoninin the hypopituitary gland, however, has not yet been elucidated. It is possible that the increase in the serotonin levels, induced by the use of SSRIs, causes an increase in the secretion on $\alpha$-MSH. Animal experiments in which the 5-HT receptors are directly activated by the serotonin agonist MK-212 show an increase in the secretion of $\alpha$-MSH. Administration of fluoxetine, on the other hand, did not influence the secretion of $\alpha$-MSH.

**Conclusion:** Reports to the Netherlands Pharmacovigilance Centre Lareb suggest a possible association between hyperpigmentation and the use of selective serotonin reuptake inhibitors.

### P075. Post-menopausal bleeding induced by Vitex agnus castus L. (Verbenaceae)

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**Introduction:** Vitamin supplements are generally considered safe. In The Netherlands, regulations only concern the allowed maximal dosages per capsule. Vitamins can be obtained not only from pharmacies and chemists, but also from supermarkets. We report a case of irregular post-menopausal bleeding in a 65-year-old woman, starting one month after having started a multivitamin preparation (Davitamon Femfit?) once daily. Ultrasound and diagnostic curettage revealed no abnormalities. The bleeding resolved after discontinuation of the vitamin preparation, containing agnus castus, several months later.

**Aim of the study:** Description of an adverse event case, involving a multivitamin supplement with phytotherapeutic additives probably causing the adverse event.

**Methods:** Analysis of the adverse event report, followed by a literature search

**Results:** Analysis of the report and subsequent searches in literature point to Vitex agnus castus L. as probable causal agent for post-menopausal bleeding. This conclusion is strongly supported by the well-documented report, including a description of the gynaecological diagnostic procedures that exclude other causes for post-menopausal bleeding. It is also supported by literature data, indicating that agnus castus is supposed to influence menstrual problems resulting from corpus luteum deficiency, including pre-menstrual symptoms, spasmodic dysmenorrhoea, insufficient lactation and certain menopausal conditions. In animal studies agnus castus diminished the release of follicle stimulating hormone and increased the release of luteinising hormone and prolactine. In humans agnus castus has been found to restore progesterone concentrations, prolong the hyperthermic phase in the basal temperature curve and restore the LH-RH test to normal.

**Conclusion:** The phytotherapeutic additive to the multivitamin supplement is believed to have caused an adverse event, which has required major diagnostic procedures. Physicians should be aware that multivitamin supplements might contain phytotherapeutic additives, which may cause adverse events

### P076. Hepatotoxicity of antibiotics. Overview of spontaneous reports.

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**Introduction:** Several antibiotics are hepatotoxic. Although hepatic side effects are less frequent than gastrointestinal or cutaneous disorders and the underlying illness may also be associated with significant hepatic injury, the potential severity of hepatic side-effects must be stressed. This abstract presents spontaneous reports in the Netherlands concerning hepatic side effects of antibiotics.

**Reports:**

— beta-lactam antibiotics: Natural penicillins are a rare cause of, mostly cytolytic, hepatic injury. Semisynthetic penicillins a more frequent cause. The liver injury results from an idiosyncratic, possible immunoallergic, reaction. Cephalosporines of the first generation rarely induce hepatitis, cephalosporins of the third generation can cause mild abnormalities in liver function tests. The Netherlands Pharmacovigilance Centre (Lareb) received most reports on amoxicilline/clavulanic acid, the majority concerned (cholestatic) hepatitis and jaundice. On cephalosporins 6 cases of liver injury were reported.

— macrolide antibiotics: Cholestatic injury during use of macrolide antibiotics are frequently described: hepatitis occurs in about 2% of patients treated over two weeks, subclinical elevation of liver enzymes in up to 15%. Some facts (e.g. eosinophilia, the usual lag period, rechallenge) favour an immunoallergic process. Lareb received 21 reports on macrolide antibiotics, concerning a variety of types of liver injury.

— tetracyclines: Tetracyclines are the only antibiotics with a direct, predictable effect on the liver. They can cause steatosis, but some cases of hepatitis are also described. The mechanism of liver injury lies in the inhibition of tetracycline of the mitochondrial oxidation of fatty acids. Lareb received 14 reports concerning liver injury as suspected adverse event of doxycycline or minocycline. The type of liver injury was diverse.

— sulphonamides (with trimethoprim): Hepatotoxicity of sulphonamides occurs in 0.06% of recipients and results commonly in both cholestasis and necrosis. Subclinical elevation of serum aminotransferases is more frequent. In most cases hepatotoxicity has been ascribed to the sulphonamide components. Liver injury