

## Elevation of liver enzyme levels during psychopharmacological treatment is associated with weight gain

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### Abstract

Increased circulating levels of liver enzymes emerging during treatment with psychotropic drugs are frequently encountered and, in general, attributed to drug metabolism or toxic effects. Because obesity was shown to be associated with elevated liver enzyme levels in different non-psychiatric study samples, we hypothesized that drug-induced weight gain might be an additional causative factor. We tested this hypothesis in 67 inpatients who received psychopharmacological treatment across five weeks. Stepwise linear regression was used to predict changes in the serum levels of aspartate-amino transferase (ASAT) and alanine-amino transferase (ALAT) by changes in the body mass index (BMI), by changes in other biological parameters related to body weight (tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ], soluble TNF receptors [sTNF-R], interleukin-6 [IL-6], leptin plasma levels) and by the respective liver enzyme baseline level. BMI changes from baseline to endpoint were significantly associated with the changes in ALAT and ASAT levels across five weeks of treatment and with ALAT and ASAT levels at the end point of the study. The baseline levels of ALAT and ASAT also had a significant impact on these liver enzyme level changes, whereas all other variables had not. These results suggest that weight gain-associated metabolic changes occurring during treatment with psychotropic drugs have consistent and clinically relevant effects on the liver.

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### 1. Introduction

Abnormal liver function tests are frequently encountered in patients receiving psychopharmacological treatment (Davis, 1991). All kinds of psychotropic drugs can elevate liver enzyme levels and have the potential to induce liver damage (Selim and Kaplowitz, 1999). Hence, the clinical relevance of liver enzyme elevation during psychopharmacological treatment is immense. Liver enzymes frequently determined in clinical practice include alanine-amino transferase (ALAT), aspartate-amino transferase (ASAT) and gamma-glutamyl transpeptidase (GGT). Increased plasma levels of ALAT and ASAT are suggestive of hepatocyte damage, GGT levels are particularly raised in alcohol-induced liver damage,

but also reflect enzyme induction within the liver (Hope et al., 1998). And indeed, the increase in GGT levels during drug treatment may reflect enzyme induction in liver microsomes where drugs are metabolized. Reactive metabolites, which may damage cell membranes and the cytoskeleton, can also lead to liver enzyme elevation (Selim and Kaplowitz, 1999). Finally, biotransformation can lead to a decrease in hepatic protective mechanisms such as glutathione (GSH) levels (Slamon and Pentreath, 2000). In general, consequences of drug metabolism are thought to be the most important causes of drug-induced elevation of liver enzyme levels.

However, in addition to drug metabolism there are other drug-induced factors, which might affect the liver. One such factor of particular importance is weight gain. Numerous psychotropic drugs induce a considerable increase in appetite and weight (Malhi et al., 2001; Pijl and Meinders, 1996; Zimmermann et al., 2003), which can lead to clinically relevant obesity. Obesity, in turn, is

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tightly associated with elevated liver enzyme levels. In different investigations – including the third US National Health and Nutrition Examination Survey (1988–1994) – this association could be established (Albert et al., 2001; Hetland et al., 1992; Ruhl and Everhart, 2003).

Therefore, we hypothesized that changes in liver enzyme levels occurring during treatment with psychotropic drugs might be related to changes in weight. We tested this hypothesis in a longitudinal approach using stepwise linear regression analysis. In addition to changes in the body mass index (BMI) as an independent variable, we included parameters which may be linked to both drug-induced weight gain and liver function. One of these is the activity of the tumor necrosis factor (TNF) cytokine system, reflected by the levels of TNF- $\alpha$  and soluble TNF receptors (sTNF-R p55 and p75), which is involved in liver diseases (Tilg, 2001) and increased by a variety of psychotropic drugs (Pollmächer et al., 1996; Pollmächer et al., 2000). As a further independent variable we included the cytokine interleukin-6 (IL-6). IL-6 was shown to play a role in hepatic inflammation and in the pathogenesis of hepatic fibrosis (Choi et al., 1994). A third cytokine included into our analysis was leptin, a fat cell-derived hormone which signals to the brain the size of the adipose tissue and which is also involved in the pathophysiology of liver diseases (Ikejima et al., 2002; Saxena et al., 2002). Leptin levels are increased by some (Brömel et al., 1998; Kraus et al., 1999) but not all (Hinze-Selch et al., 2000a; Kraus et al., 2002) psychotropic drugs, which induce weight gain. To investigate whether the liver enzyme levels prior to starting psychopharmacological treatment have any influence on the time course of these enzymes we also used the baseline levels of ALAT and ASAT as independent variables of the regression analysis.

## 2. Materials and methods

### 2.1. Patients

In the framework of a clinical study investigating peculiarities of drug-induced weight gain we included 33 female and 34 male consecutively admitted inpatients (mean age:  $44.4 \pm 16$  years) who received a stable psychopharmacological treatment at the Max Planck Institute of Psychiatry over at least five consecutive weeks. After complete description of the study, all patients gave written informed consent to participate in the investigation, which had been approved by an independent ethics committee. Patients suffered from various psychiatric disorders, mainly affective or schizophrenic disorders.

### 2.2. Experimental procedure

Fasting venous blood samples were drawn in the morning between 08:00 and 09:00 and patients were

weighed at baseline and at the end of five consecutive weeks. The body mass index (BMI) was calculated by dividing the weight (in kilograms) by the squared height (in meters). Blood was stabilized with sodium ethylenediaminetetraacetic acid (1 mg/ml) and aprotinin (300 kIU/ml) and immediately centrifuged and the plasma was frozen to  $-20$  °C. Cytokines were measured with commercial enzyme-linked immunosorbent assays (TNF- $\alpha$ , sTNF-R p55, sTNF-R p75 and IL-6 [Medgenix Diagnostics, Brussels, Belgium]) or with a radioimmunoassay (leptin [Linco Research, Missouri, USA]). For all assays the intra- and inter-assay coefficients were below 7% and 9%, respectively. ASAT, ALAT and GGT activity levels were measured by photometry according to the International Federation of Clinical Chemistry (IFCC) methods for the measurement of enzymes (Bergmeyer et al., 1986a,b; Shaw et al., 1983). ALAT levels of 22 U/l and ASAT levels of 18 U/l were considered as upper normal limit.

After baseline evaluation, medication was started and the dosage was adjusted according to clinical needs. Patients continuously received the medication listed in Table 1 for five weeks. Thirty eight patients received a combination of two, five patients a combination of three of these drugs. Specific drugs for every patient were chosen based on clinical considerations exclusively. Some of the patients had previously been exposed to antidepressants or antipsychotics, but at baseline all subjects were free of antidepressants, neuroleptics or mood stabilizers for at least one week.

### 2.3. Statistics

Descriptive statistics were calculated for the BMI, ASAT, ALAT and GGT levels. We compared the liver enzyme levels at baseline of overweight and obese patients (BMI more than  $25 \text{ kg/m}^2$ ) with the respective values of normal and underweight patients using an analysis of variance (ANOVA). The influence of gender on ASAT, ALAT and GGT levels at baseline and at week five (end point) and ASAT, ALAT and GGT level changes across five weeks was tested using an ANOVA. ANOVA for repeated measurements was performed for the time course of liver enzyme, TNF- $\alpha$ , sTNF-R p55, sTNF-R p75, leptin and IL-6 levels, with gender and smoking as between-subjects factors, and the BMI at baseline and age as covariates. ANOVA for repeated measurements was also performed for the time course of the BMI, with gender and smoking as between-subjects factors and age as covariate. Stepwise linear regression analysis was used to analyze the association of the liver enzyme level changes from baseline to end point (or from baseline to week three, see below) with changes in BMI, with changes in the plasma levels of TNF- $\alpha$ , sTNF-R p55, sTNF-R p75, IL-6 and leptin and with the baseline level of the respective liver enzyme (ALAT or

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