# Treating major depressive episodes with antidepressants can induce or worsen metabolic syndrome: results of the METADAP cohort

Recent data (1-4) show a high comorbidity between major depressive disorder and metabolic syndrome (MetS) (5), a cluster of risk factors for cardiovascular diseases and type 2 diabetes including high waist circumference, high blood pressure, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, and high fasting plasma glucose.

In a context of increasing prescription of antidepressant medication (6) and evidence of weight gain induced by antidepressants (7), the impact of antidepressant treatment on MetS has to be clarified. Indeed, there has been no prospective study of reasonable sample size and duration addressing the incidence of MetS in patients with major depressive episode treated with antidepressants.

This question was addressed in the METADAP, a 6-month prospective, multicentric, real-world treatment observational cohort study of 624 patients with a diagnosis of major depressive disorder and a current major depressive episode. Data were collected from November 2009 to March 2013 in six university psychiatry departments in France.

Consecutive in- or out-patients, aged 18 to 65 years, with a current major depressive episode in a context of major depressive disorder (with a minimum score of 18 at the Hamilton Depression Rating Scale-17, HDRS-17) were assessed for MetS at the start of the index antidepressant treatment (M0), and one (M1), three (M3) and six (M6) months later. All of them provided their written informed consent.

Patients with psychotic symptoms, bipolar disorders, psychotic disorders, eating disorders, current substance abuse or dependence, pregnancy, organic brain syndromes or severe unstable medical conditions were not included. Patients receiving antipsychotics or mood stabilizers before inclusion and/or for 4 months or more during the last year were also excluded. Antipsychotics, mood stabilizers and stimulants were not permitted during the study, because of their metabolic effects. Benzodiazepines at the minimum effective dose and for the minimum time period and psychotherapies were allowed. The index antidepressant treatment had to be a monotherapy. The drug and its dose were left to the treating psychiatrist, using "real world" treatment options.

MetS was diagnosed according to the International Diabetes Federation definition (8). Participants had to have fasted and abstained from strenuous physical activity for 8 hours before examination. Triglycerides, HDL cholesterol and fasting plasma glucose levels were assessed using routine standardized laboratory methods. Thereafter, an assistant investigator blind to the major depression assessment measured waist circumference and blood pressure.

Mixed-effects multivariate models were used, because they are a well-accepted method for analyzing longitudinal clinical data in which missing or mistimed observations are present (9). All regression models included main effects for time since initiation of current antidepressant treatment, age, gender, HDRS-17 score at baseline, lifetime duration of prior major depressive disorder, lifetime duration of prior antidepressant medication, antidepressant-free period before inclusion, and current antidepressant classes.

Of 689 pre-included patients, 643 were included, of whom 19 had major deviations to the protocol. Thus, 624 patients were analyzed. Six had missing data for MetS at baseline.

Patients' mean age was 45.6±13.2 years; 68.7% were women, 87.5% were inpatients at baseline. Their mean HDRS-17 score at baseline was 24.7±5.0. Their mean number of previous major depressive episodes was 1.9±2.1. The average lifetime duration of major depressive disorder before inclusion was 11.5±12.2 years. The lifetime duration of antidepressant drug treatment before inclusion was 2.3±4.1 years.

Upon inclusion, 22.7% of patients were antidepressant naïve. The administered antidepressant was a selective serotonin reuptake inhibitor (SSRI) in 38.9% of cases, a serotonin norepinephrine reuptake inhibitor (SNRI) in 38.3%, a tricyclic antidepressant (TCA) in 8.8%, and another one in 14.0%. The mean duration of follow-up was 4.9±4.6 months. The drop-out rate was 25.9% before M1, 21.8% between M1 and M3, and 14.3% later. The main reasons for drop-out were antidepressant change (28.4%), prescription of antipsychotics or mood stabilizers (29.4%), and lost to follow-up (20.4%).

In patients without MetS at baseline (N=442, 70.8%), the incidence of MetS was 11.7% at M3 and 16.5% at M6. This increase was significant (mixed-effect multivariate logistic regression: OR=2.29, 95% CI: 1.69-3.10, $p<0.0001$). It was observed within both the SSRI (0% to 16.2%, $p<0.001$) and the SNRI group (0% to 16.1%, $p=0.001$). This increase was independent from other factors, such as age, lifetime duration of prior antidepressant medication, and presence of an antidepressant-free period at baseline.

The number of altered components of MetS significantly increased with time (M0: 1.2±0.9, M3: 1.3±1.1, M6: 1.5±1.2; mixed-model multivariate Poisson regression: incident risk ratio, IRR=1.06, 95% CI: 1.02-1.09, $p<0.0001$). It

was significantly higher in patients treated with SNRIs than in those treated with SSRIs (IRR=1.45, 95% CI: 1.16-1.80, p=0.001), and it was lower amongst patients who were antidepressant-free at baseline (IRR=0.81, 95% CI: 0.65-0.99, p=0.03). These effects were independent from each other, from age and gender.

In patients with MetS at baseline, mixed-effect multivariate linear regressions showed significant increases over time of supine blood pressure (M0: 123.2±16.4 mmHg, M3: 124.8±13.9 mmHg, M6: 126.8±15.0 mmHg, $p<0.05$) and fasting plasma glucose (M0: 0.98±0.29 g/l, M3: 1.07±0.48 g/l, M6: 1.03±0.31 g/l, $p<0.01$), which were independent from other factors.

The highlight of this study is the early and significant incidence of MetS after initiation of treatment with antidepressants. The majority of cases occurred in the first three months of treatment. A significant worsening of MetS was also observed in patients who already had the syndrome at baseline.

Taken together, these results suggest that treating major depressive episodes with antidepressants can induce or worsen MetS. Specific recommendations for the prevention of MetS in patients with major depressive disorder receiving antidepressant medication are needed. Further studies assessing the underlying mechanisms of this phenomenon are warranted.

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