Post-hoc analysis of placebo-controlled trials in children and adolescents with depression

STASTICIAL ANALYSIS PLAN

Introduction

The possible usefulness of SSRIs and SNRIs in treating depression in children and adolescents remains a highly controversial subject. The aim of this project is to shed further light on the following issues: i) do data from available trials indicate than SSRIs are superior to placebo in reducing the rating of one or several items on depression rating scales in children and adolescents?, ii) is a possible effect associated with age?, iii) is a possible effect associated with gender?, iv) is a possible effect associated with baseline symptom profile?

Data source

Four studies on citalopram and escitalopram in child and adolescent depression will be analyze:

1. SCT-MD-15: A double-blind, placebo-controlled evaluation of the safety and efficacy of escitalopram in pediatric depression

2. CIT-MD-18: A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of citalopram in children and adolescents with depression.

3. SCT-MD-32: A double-blind, flexible-dose study of escitalopram in pediatric patients with major depressive disorder.

4. 94404: A randomized, double-blind, placebo-controlled study of citalopram in adolescents with major depressive disorder.

For all studies the sum rating of the CDRS and MADRS rating scales, as well as individual items from these scales, will be analyzed. Various secondary measures may be assessed as well.

Analysis objectives

To assess the severity of individual items at baseline as well as the possible influence of age and gender on baseline symptom profile. To assess dropout rates. To analyze treatment outcome as reflected by reductions in mean rating of individual items as well as of sum scores. To analyze treatment outcome reflected by response and/or remission at endpoint (with respect to both individual items and sum scores). To analyze the possible influence of age, gender and baseline symptom profile on all measures of efficacy.

Analysis sets and subgroups

All randomized patients from the respective studies are to be included. *First*, we plan to assess the baseline prevalence and severity of all individual items of the respective scales, as well as the sum score, and to what extent these measures are associated with age and gender. *Second*, we plan to calculate outcomes for SSRI- and placebo-treated patients for

each age (as coded in the original datasets, but also rounded to the closest whole number) with a further subdivision by gender. Outcome assessment will include i) mean reduction of total points on the rating scale(s) used, ii) mean reduction of individual items on these scales, ii) response defined as 50% reduction of points on total score or individual items, iii) remission defined as <=28 points on the CDRS-R scale or <=12 points on the MADRS or lowest possible rating (symptom not present) for individual items. These analyses will also be performed using age as a linear variable. *Third*, we plan to assess the number of dropouts per week and if these are associated with age and gender. All analyses will be performed both for each individual study and, when possible, on a pooled population. These results will further be subjected to meta-analysis (mean reduction of points) and pooling (response/remission) together with other studies regarding the efficacy of SSRIs/SNRIs in child and adolescent depression, i.e. on paroxetine, duloxetine, fluoxetine and sertralin.

Analyses aiming to address the possible association between baseline symptom profile and outcome cannot be finally designed until baseline data have been inspected.

Endpoints and covariates

We plan to assess outcomes for each visit; however, week 8 is considered endpoint as in the primary studies 1-3. For study 94404, week 9 will be considered endpoint but the observation at week 12 will also of be analyzed. Covariates may include baseline CDRS/MADRS total score, baseline score on individual CDRS/MADRS items, visit number, study, investigator, age, gender and data on co-morbidities.

Statistical procedures

All analyses are to be performed for each age and gender and for individual studies, as well as for pooled populations. For baseline measures, we will quantify the number of patients experiencing each score on all individual items from the psychometric scale(s) used as well as mean scores. A general linear model will be used for continuous measures, i.e. reduction of points on psychometric scales. Differences between treatment groups will be contrasted by using differences of least mean squares estimates (LSM). Effect sizes (Cohen's *d*) will be calculated using the LSM differences at each time point of interest divided by the root of the variance for the corresponding observation. For response and remission criteria, we will calculate number and percentage of patients fulfilling these criteria by endpoint, and analyze differences using odds ratios (OR).

Handling of missing data and sensitivity analyses

For all outcome measures, we plan to conduct both observed cases (OC) and last observation carried forward (LOCF) analyses. Mixed modelling using repeated measures (MMRM) will be used when not restricted by the size of the groups analyzed.

Additional analyses

An important advantage of this kind of post hoc data mining is that one is free to improvise depending on what the data reveal. Thus, it cannot be excluded that some additional analyses may be added to the above-mentioned plan as works is in progress.