

# **Dose-response relationship of new generation antidepressants: Protocol for a systematic review and dose-response meta-analysis**

## **REVIEW QUESTION**

What is the dose-response relationship for selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs) and other second-generation antidepressants?

## **METHODS**

This study is a derivative study from the systematic review and network meta-analysis of all second-generation and selected first-generation antidepressants licensed for the acute phase treatment of major depression in USA, Europe or Japan (Furukawa, Salanti et al. 2016, Cipriani, Furukawa et al. 2018).

### **Data sources**

We will include fixed-dose double-blind, randomized controlled trials (RCTs) comparing antidepressants among themselves or with placebo as oral monotherapy for the acute phase treatment of adults (aged 18 years or older) of both sexes, with a primary diagnosis of major depressive disorder according to standard operationalized diagnostic criteria (Feighner Criteria, Research Diagnostic Criteria, DSM-III, DSM-III-R, DSM-IV, DSM-5, ICD-10). Trials of antidepressants for depressive patients with a serious concomitant physical illness will be excluded.

We have searched Cochrane Central Register of Controlled Trials, CINAHL, EMBASE, LILACS, MEDLINE, MEDLINE In-Process, PsycINFO, AMED, the UK National Research Register, and PSYNDEX from the date of their inception to Jan 8, 2016. We have scrutinized reference lists of all relevant papers. We have searched files of the national drug licensing agencies in six countries (USA, UK, Netherlands, Sweden, Japan and Australia), the European Medicines Agency and several trial registries for published, unpublished and ongoing RCTs. We contacted all pharmaceutical companies marketing second-generation antidepressants and asked for supplemental unpublished information about their pre-marketing and post-marketing trials. We contacted the National Institute for Health and Care Excellence (NICE, UK), the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG, Germany), and any other relevant organizations and individuals for any additional information not already identified. We used broad search terms for depression (*depress\** or *dysthymi\** or *adjustment disorder\** or *mood disorder\** or *affective disorder* or *affective symptoms*) in conjunction with generic and commercial names of all antidepressants under review. We imposed no language restriction.

### **Selection criteria for the study**

This study focuses on second-generation antidepressants, as dose-response relationships may be different for different classes of antidepressants (Adli, Baethge et al. 2005). The antidepressants of interest in this study therefore will include: SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), SNRIs (desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine), and others (agomelatine, bupropion, mirtazapine, reboxetine, vilazodone, vortioxetine).

In order to examine dose-response relationships we will include all trials from the larger dataset above that compared two or more different fixed doses (including placebo, which is 0 mg) of the above antidepressants within a trial. We will include arms within, below or above the dose

ranges licensed by drug approval agencies in USA, Europe or Japan.

### **Data extraction and risk of bias assessment**

Two independent reviewers have extracted data and assessed the risk of bias of the included studies. In case of disagreement, a third member of the review team was consulted and made the final decision. (Furukawa, Salanti et al. 2016)

### **Primary outcomes**

The primary outcomes of interest in this study are the following benefit as well as harm outcomes at the time point as close to 8 weeks (range 4-12 weeks) as possible in each included study.

- 1 Response, defined as 50% or greater reduction on an observer-rated scale for depression
- 2 Dropouts for adverse effects
- 3 Dropouts for any reasons, interpreted as an overall index of treatment acceptability

We will take the number of randomized patients as the denominator for all outcomes; those who had been randomized but not accounted for in the original study will be assumed to have dropped out for some reason other than adverse effects and without responding.

### **Statistical analyses**

#### ***Meta-analysis of dose-response curves***

We will synthesize dose-response association using meta-analysis (Crippa and Orsini 2016), as implemented in the *dosres* package in R (Crippa and Orsini 2016). Given the clinical and methodological heterogeneity likely present in the included studies, we will use the random effects model. This model has recently been applied to estimate dose-response relationships in various settings (Crippa, Discacciati et al. 2014, Di Giuseppe, Crippa et al. 2014, Larsson, Crippa et al. 2015, Smith, Crippa et al. 2016, Vinceti, Filippini et al. 2016, Aneni, Crippa et al. 2017, Crippa, Larsson et al. 2018). To allow for flexibility we will use cubic splines to model the dose-response association.

#### ***Stages of data synthesis***

On the one hand, different drugs and different classes of antidepressants may have different dose-response relationships. On the other, extant RCTs are likely too few to allow precise estimation of dose-response for any single drug and meta-analysis across different drugs and different classes of drugs is necessary to elucidate the underlying dose-response relationships. This study therefore takes the following stepwise approach to data synthesis while paying due attention to heterogeneity in the included studies.

- 1 Dose-response synthesis for each drug separately
- 2 Dose-response synthesis for all drugs after dose conversion

There are several methods to define and calculate dose equivalence (Patel, Arista et al. 2013). We will use the most recent and comprehensive review of dose equivalence of antidepressants (Hayasaka, Purgato et al. 2015), which used the method that was originally used to calculate dose equivalence of antipsychotics by assuming the optimum doses found in double-blind flexible-dose trials of various antipsychotics to be equivalent (Davis 1974). Previous studies on dose-response of antidepressants used similar but different conversion algorithms (Bollini, Pampallona et al. 1999, Baker and Woods 2003, Jakubovski, Varigonda et al. 2016). Where no empirical data for dose conversion were available, we will assume the Daily Defined Dose (DDD), the average maintenance dose per day calculated from the dosage recommendations in each drug's product information according to WHO (WHO Collaborative Centre for Drug Statistics Methodology 2006), to be equivalent. We will test the robustness of our primary dose conversion, using Hayasaka et al (Hayasaka, Purgato et al. 2015) supplemented by DDD (WHO Collaborative Centre for Drug Statistics Methodology 2006), in a sensitivity analysis.

## Sensitivity analyses and subgroup analyses

In order to ascertain the robustness of the primary analyses, we will conduct the following sensitivity analyses.

- 1 To test the influence of the dose conversion algorithms
  - 1.1 Using the algorithm by Jakubovski et al (Jakubovski, Varigonda et al. 2016), supplemented by DDD (WHO Collaborative Centre for Drug Statistics Methodology 2006)
- 2 To test the stability of the shape of the spline curves
  - 2.1 Setting knots for spline curves at different doses: We will examine the goodness-of-fit statistics of different models (Discacciati, Crippa et al. 2017).
  - 2.2 Limiting the ranges of examined doses
    - 2.2.1 Analyses limited to the licensed dose range, i.e. between 20 and 80 mg of fluoxetine equivalents)
    - 2.2.2 Analyses limited to the dose range between 0 mg and 30 mg of fluoxetine equivalents

We will conduct the following subgroup analyses.

- 1 Analyses limited to different classes of antidepressants
  - 1.1 SSRIs
  - 1.2 SNRIs

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eTable 1. Dose equivalence according to previous studies.

Antidepressant	Bollini	Baker	Jakubovski	Hayasaka	DDD	Current study
agomelatine	-	-	-	26.6	25	26.6
bupropion	-	-	-	174.3	300	174.3
citalopram	30	-	33.3	-	20	20
desvenlafaxine	-	-	-	-	50	50
duloxetine	-	-	-	-	60	60
escitalopram	-	-	16.7	9	10	9
fluoxetine	20	20	20	20	20	20
fluvoxamine	100	-	100	71.7	100	71.7
milnacipran	100	-	-	-	100	100
mirtazapine	-	-	-	25.5	30	25.5
paroxetine	20	30	20	17	20	17
reboxetine	-	-	-	5.7	8	5.7
sertraline	83	100	120	49.3	50	49.3
venlafaxine	100	-	-	74.7	100	74.7
vilazodone	-	-	-	-	10	10
vortioxetine	-	-	-	-	10	10