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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Netherlands, Sweden, Japan and Australia), the European Medicines Agency and several trial registries for published, unpublished and ongoing RCTs. We contacted all pharmaceutical companies marketing second-generation antidepressants and asked for supplemental unpublished information about their pre-marketing and post-marketing trials.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 will include those most often prescribed in UK: namely, SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, sertraline), venlafaxine, and mirtazapin. 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.

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 abide by the intention-to-treat principle by taking 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

Multivariate dose-response meta-analysis

We will apply the multivariate dose-response meta-analysis(Crippa and Orsini 2016), using the *dosres* package in R (Crippa and Orsini 2016). Given the clinical and methodological heterogeneities 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 meta-analyses (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).

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. This study therefore takes the following stepwise approach to data synthesis while paying due attention to heterogeneity among the included studies.

1 Dose-response analysis for single drugs
2 Dose-response analysis for all SSRIs after dose conversion, as they share a key therapeutic mechanism

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

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)
   1.2 Using the conversion based on average doses actually prescribed for major depression (Olfson and Marcus 2009)
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).

CHANGES IMPLEMENTED ON JAN 2019

We have decided to focus on the antidepressants most commonly prescribed in UK, and have therefore removed mention of the other drugs.

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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