Systematic evaluation of the „efficacy-effectiveness gap“ in the treatment of depression with Venlafaxine and Duloxetine
(Protocol for a systematic review, Ulm, February 20th, 2013)

Markus Kösters, Ann-Christien Holtrup, Ines Fiedler, Thomas Becker

The study is funded by the young scientists’ programme of the German network 'Health Services Research Baden-Württemberg' of the Ministry of Science, Research and Arts in collaboration with the Ministry of Employment and Social Order, Family, Women and Senior Citizens, Baden-Württemberg."

The protocol is an abbreviated translation of the German protocol, which was submitted to the young scientists’ programme office in July 2011.

Contact Person:

Dr. Markus Kösters
Department Psychiatry II, Ulm University
Bezirkskrankenhaus Günzburg
Ludwig-Heilmeyer-Str. 2
D-89312 Günzburg
Markus.Koesters@uni-ulm.de
Phone: ++49-8221-96-2869
Objectives

(1) A systematic collection and meta-analysis of all prospective nonrandomized or uncontrolled studies, which investigate efficacy of Duloxetine or Venlafaxine in the treatment of depression.

(2) To quantify and evaluate differences of effect-sizes of randomized controlled trials (RCTs) and non-RCTs and to identify factors determining differences of treatment effects between clinical trials and everyday practice (e.g. dosage, compliance, severity of illness)

Method

Design

Systematic review and meta-analyses

Included studies

The review will include all prospective trials (RCTs, nonrandomised and uncontrolled) which evaluated the treatment effects of Duloxetine and Venlafaxine in depressed patients and provided data to calculate pre-post effect sizes or response rates.

Studies in which Duloxetine or Venlafaxine are used as concomitant antidepressants will be excluded. Furthermore, case-reports, studies without full publications (e.g. conference abstracts) and double publications will also be excluded, as well as studies pooling data from more than one trial will also be excluded.

Literature search:

The electronic search is based upon a sensitive search strategy (see Appendix) in the electronic databases EMBASE, Medline, PsycLit, PsychInfo, PSYNDEXplus and the Cochrane Central Register of Controlled Trials (Central). The search will be supplemented by a search in manufacturer databases (e.g. lillitrials.com) and in study registries (e.g. clinicaltrials.gov). Furthermore references of included studies will be screened for additional relevant trials.

Study selection:

In the first step of the study selection, two independent researchers will select trials meeting the inclusion criteria based on title and abstracts. All studies rated as potentially relevant by one of the researchers will be screened in full text to finally decide about the inclusion. Disagreements will be resolved by discussion.
Data collection

Based on publication guidelines for observational studies (1) and available measuring instruments for trial quality of non randomised trials (2), a coding schedule will be developed which contains items to describe possible differences between treatments in RCTs and everyday clinical practice. These items (e.g. selection of participants, setting etc.) will be derived from literature (e.g. 3, 4). We will calculate a sum score from these items, which describes proximity to everyday conditions. Two independent researchers will appraise studies with regards to quality and proximity to everyday conditions. Data extraction will be done by one researcher and checked by a second.

Data to calculate pre-post effect sizes for depressive symptoms, as well as response rates, overall dropout rates and dropout rates due to adverse events will be extracted.

Data analyses

Effects will be calculated as pre-post effect sizes. To calculate the variance of pre-post effect sizes pre-post correlation needs to be taken into account, but it’s rarely reported. Therefore, sensitive analyses will conduct calculations with assumed correlations of 0.4, 0.9 and statistical independence. The primary outcome will be the depression scale pre post effect size after acute therapy (≤12 weeks). Preference will be given to endpoint data from the Hamilton Depression Rating Scale (HAMD) and the Montgomery-Asberg Depression Scale (MADRS), because these scales are most common in antidepressant research. In case of different groups or treatment arms of one intervention ( duloxetine or venlafaxine) within a study (e.g. dosing, subgroup of patients), these groups will be combined for the primary analyses, resulting in one effect size per intervention and study.

Effect sizes will be weighted by the inverse variance and aggregated in random effect models. Study heterogeneity will be assessed by $I^2$-parameter and tested by $\chi^2$-tests. To assess publication bias graphical (funnel plots) and statistical methods (Egger’s regression test) will be used. Influences of study types on effect sizes will be estimated by subgroup analyses. The influences of the sum score (see above) on the effect size will be explored by a meta-regression. Depending on study heterogeneity, explorative subgroup analyses and meta-regressions will be carried out to evaluate influences of trial quality, sample characteristics etc. on effect sizes. Data analyses will be analysed by Comprehensive Meta Analysis (5) or R (6).

References


---

1 This is a deviation of the German protocol. The German protocol states that effect sizes for response and drop-out rates will be calculated as Risk Ratios. As no comparisons will be made between groups, it is impossible to calculate risk ratios. Absolute rates will be used instead in exploratory analyses. The primary outcome was clarified during data extraction before the beginning data analyses.


APPENDIX

Search strategy

1  exp Neurotic Disorders/
2  exp Depressive Disorder/
3  exp Depression/
4  depress$.mp.
5  neurotic disorder$.mp.
6  seasonal affective disorder$.mp.
7  dysthymi$.mp.
8  melanchol$.mp.
9  or/1-8
10  (Duloxetin$ or Cymbalta).mp.
11  (Venlafaxin$ or Dobupal or Effexor or efexor or Trevilor or Vandral).mp.
12  10 or 11
13  clinical trial.mp.
14  clinical study.mp.
15  exp clinical trial/ or comparative study/ or evaluation studies/
16  efficacy.mp.
17  effectiveness.mp.
18  or/12-17
19  9 and 12 and 18
20  limit 19 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)" or "300 adulthood <age 18 yrs and older>" or 320 young adulthood <age 18 to 29 yrs> or 340 thirties <age 30 to 39 yrs> or 360 middle age <age 40 to 64 yrs> or "380 aged <age 65 yrs and older>" or "390 very old <age 85 yrs and older>") [Limit not valid in Ovid MEDLINE(R),CCTR,Embase,PsycINFO,PSYNDEXplus Literature and Audiovisual Media; records were retained]
21  limit 20 to humans [Limit not valid in CCTR,PsycINFO,PSYNDEXplus Literature and Audiovisual Media; records were retained]
22  limit 21 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter
study) [Limit not valid in PsycINFO, PSYNDEXplus Literature and Audiovisual Media; records were retained]

23  limit 22 to adulthood <18+ years> MEDLINE(R), CCTR, EMBASE, PSYNDEXplus Literature and Audiovisual Media; records were retained

24  limit 23 to human [Limit not valid in CCTR, PSYNDEXplus Literature and Audiovisual Media; records were retained]

25  limit 24 to (adult <18 to 64 years> or aged <65+ years>) [Limit not valid in Ovid MEDLINE(R), CCTR, PsycINFO, PSYNDEXplus Literature and Audiovisual Media; records were retained]

26  limit 25 to humans [Limit not valid in CCTR, PsycINFO, PSYNDEXplus Literature and Audiovisual Media; records were retained]

27  limit 26 to ("0400 empirical study" or "0430 followup study" or "0450 longitudinal study" or "0451 prospective study" or "1800 quantitative study" or "2000 treatment outcome/randomized clinical trial") [Limit not valid in Ovid MEDLINE(R), CCTR, EMBASE, PSYNDEXplus Literature and Audiovisual Media; records were retained]

28  limit 27 to humans [Limit not valid in CCTR, PsycINFO, PSYNDEXplus Literature and Audiovisual Media; records were retained]

29  remove duplicates from 28