PROFESSOR TOSHI A. FURUKAWA (Orcid ID : 0000-0003-2159-3776)

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No benefit from flexible titration above minimum licensed dose in prescribing antidepressants for major depression

Toshi A. Furukawa, MD, PhD* †

Departments of Health Promotion and Human Behavior and of Clinical Epidemiology, Kyoto University Graduate School of Medicine / School of Public Health, Kyoto, Japan

furukawa@kuhp.kyoto-u.ac.jp

Georgia Salanti, PhD*

Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland

georgia.salanti@ispm.unibe.ch

Philip J. Cowen, MD, FRCPsych

Department of Psychiatry, Warneford Hospital, University of Oxford, Oxford, UK

phil.cowen@psych.ox.ac.uk

Stefan Leucht, MD
Department of Psychiatry and Psychotherapy, School of Medicine, Technical University of Munich, Munich, Germany
stefan.leucht@tum.de

Andrea Cipriani, MD, PhD
Department of Psychiatry, Warneford Hospital, University of Oxford, Oxford, UK
Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK
andrea.cipriani@psych.ox.ac.uk

* equal contribution

† Corresponding author: Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine / School of Public Health, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501 JAPAN

ABSTRACT

Background: In fixed dose antidepressant trials, the lower range of the licensed dose achieves the optimal balance between efficacy and tolerability. Whether flexible upward titration while side effects permit provides additional benefits is unknown.

Methods: We did a systematic review of placebo-controlled randomised trials that examined selective serotonin reuptake inhibitors (SSRIs), venlafaxine or mirtazapine in the acute treatment of major depression. Our primary outcome was response, defined as 50% or greater reduction in depression severity. Secondary outcomes included dropouts due to adverse effects and dropouts for any reason. We conducted random effects meta-analyses to calculate the ratios of odds ratios (RORs) between trials comparing the flexible dose titrating above the minimum licensed dose against placebo and those comparing the fixed minimum licensed dose against placebo.

Results: We included 123 published and unpublished randomized controlled trials (29,420 participants). There was no evidence supporting efficacy of the flexible dosing over the fixed low dose of SSRIs (ROR 0.96, 95%CI: 0.73 to 1.25), venlafaxine (1.24, 0.96 to 1.60) or mirtazapine (0.77, 0.33 to 1.78). No important differences were noted for tolerability or for any subgroup analyses except the superior efficacy of venlafaxine flexible dosing between 75-150 mg over the fixed 75 mg (1.30, 1.02 to 1.65).

Conclusion: There was no evidence to support added value in terms of efficacy, tolerability or acceptability of flexibly titrating up the dosage over the minimum licensed dose of SSRIs or mirtazapine. For venlafaxine, increased efficacy can be expected by flexibly titrating up to 150 mg.

Keywords:

Major depressive disorder; Antidepressivee agents; Flexible dosing; Fixed dosing

Summations:

- In the acute phase treatment of major depression, flexibly titrating the dose while side effects permit above the minimum licensed dose in SSRIs or mirtazapine provides no increase in efficacy and acceptability and no decrease in tolerability over fixed prescribing at the minimum dose.
- For venlafaxine, flexible titration up to 150 mg/day but not beyond was more efficacious than fixed dose at 75 mg/day.

Considerations:

- The comparison between the flexible dosing and the fixed dosing was across studies and not randomized within studies and therefore may be subject to confounding.
- For some comparisons, there were limited numbers of studies and the confidence intervals of the pooled estimates were wide.
- Because the findings are based on aggregate data meta-analysis, the conclusions apply to the group average: for individual patients the dosage needs be adjusted around the optimum group average, taking into account such individual characteristics as age, body weight, comorbidities or past experiences with similar drugs.

INTRODUCTION

Antidepressant pharmacotherapy is currently the most widely used treatment for depression. Second-generation antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), are recommended as first-line options in the pharmacological management of major depression (1).

Every antidepressant has a range of licensed dosages. For example, in the case of fluoxetine, the most classical SSRI, the dose range approved by the US Food and Drug Administration is between 20 to 80 mg/day. International guidelines recommend conflicting strategies as to where in this wide range the clinicians should target the dosage (1, 2). Our recent dose-response meta-analysis of SSRIs has shown that both response and remission gradually increase up to doses between 20 and 40 mg fluoxetine equivalents, with no further increase or even a slight decrease at higher doses. Dropouts due to adverse effects showed a steep increase through the examined range. Consequently, the lower range of the licensed doses (between 20 and 40 mg fluoxetine equivalents) achieves the optimum balance between efficacy, tolerability and acceptability. (3).

These findings were based on fixed dose randomized controlled trials (RCTs) (3). However, fixed-dose studies typically use rapid or no titration and this may exaggerate dropouts and underestimate efficacy (3-5). By contrast, the flexible dose regimen that titrates upward or downward in view of each patient's response and side effects may decrease dropouts and increase response. Real-world practices are better represented by such flexible-dose studies and consequently the optimal target dose range in practice could be higher than those suggested by fixed regimen studies (4). However, there has been to date no empirical data to support this claim.

This study aims to examine whether flexible increasing above the minimum licensed dose is more beneficial than prescribing the fixed minimum licensed dose. The two approaches are compared in terms of efficacy, tolerability and acceptability. As only few studies have directly compared flexible and fixed regimens, we will compare them indirectly via placebo.

METHODS

Study search and selection

This study uses the trials identified in a previously published systematic review with network meta-analysis (6, 7). We have searched the Cochrane Central Register of Controlled Trials, CINAHL, Embase, LILACS, MEDLINE, MEDLINE In-Process, PsycINFO, AMED, the UK National Research Register, and PSYNDIX, as well as the website of the national drug licensing agencies in six countries (USA, UK, Netherlands, Sweden, Japan and Australia), the European Medicines Agency, and trial registries for published, unpublished and ongoing RCTs. We contacted relevant pharmaceutical companies and asked for supplemental unpublished information as well as the National Institute for Health and Care Excellence (UK), the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Germany) and relevant individuals for additional information. Search was conducted with broad search terms for depression (depress* or dysthym* or adjustment disorder* or mood disorder* or affective disorder* or affective symptom*) in combination with generic and commercial names of all antidepressants under consideration. We also scrutinised reference lists of all the identified documents. There was no language restriction. The search was last updated on January 8, 2016. The complete dataset is accessible on Mendeley (https://data.mendeley.com/datasets/83rthbp8ys/2). There was no indication of small study effect or reporting bias in this dataset (6).

We had originally included double-blind, randomised controlled trials (RCTs) comparing antidepressants among themselves or against placebo in the acute phase treatment of adults (aged 18 or older) of both sexes, with a primary diagnosis of major depressive disorder according to standard operationalised diagnostic criteria. Studies focusing on patients with depression with another psychiatric disorder or a serious concomitant physical illness as well as those on bipolar, chronic, or treatment-refractory depression were excluded.

The current study builds upon our previous dose-response meta-analyses (3) that focused on the most frequently prescribed new-generation antidepressants in the UK according to Open Prescribing (8), namely five SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, sertraline), venlafaxine and mirtazapine. In this study we included all RCTs that administered these drugs either on a fixed dose regimen at their respective minimum licensed dose or a flexible dose regimen that allowed titration above the minimum dose, side effects permitting. The lowest licensed dosage was 20 mg for citalopram, 10 mg for

escitalopram, 20 mg for fluoxetine, 20 mg for paroxetine (paroxetine CR was calculated into paroxetine dosage by multiplying by 0.8 (9)), 50 mg for sertraline, 75 mg for venlafaxine and 15 mg for mirtazapine. The fixed dose studies in the current analyses were therefore those which compared these dosages against placebo. The flexible dose studies were then defined as those which compared drug arms which allowed upward titration beyond these minimum dosages against placebo.

Outcomes

Our primary outcome was response, defined as 50% or greater reduction from baseline on an observer-rated depression severity scale. Secondary outcomes included depression severity measured on a continuous scale, dropouts due to adverse effects as an index of treatment tolerability, and dropouts for any reason as an index of overall treatment acceptability. We recorded the outcomes as close to 8 weeks as possible for all analyses (range: 4-12 weeks).

When depressive symptoms had been measured with multiple instruments, we followed a predefined hierarchy prioritizing the Hamilton Rating Scale for Depression (HAMD), then Montgomery-Åsberg Depression Rating scale, then any other validated observer-rated measure. In the absence of information or supplemental data from the authors, response rates were calculated according to a validated imputation method (10). When SDs were not reported, but SEs, t-statistics or p values were reported, they were transformed to SDs (11). When SDs were not available and were not provided by the authors upon request, the mean value of known SDs from the included studies were used (12). A sensitivity analysis in the original network meta-analysis confirmed the robustness of these imputations (6). We set the number of patients who were randomly assigned as the denominator for all outcomes, assuming that patients lost to follow-up had dropped out without experiencing response or dropout due to adverse effects (13). When there were discrepancies in the reported data across multiple sources, we gave priority to unpublished information (7). Study selection and data extraction were conducted by at least two independent raters; any discrepancy was resolved by consensus of the study team. More detail about data extraction of outcomes can be found in the previous publications (3, 6, 7).

We set the dichotomous measure of response, rather than the continuous measure of depression severity, as our primary outcome in concert with the original network meta-analysis (6, 7), because the former is more clinically interpretable than the latter and also

because the former enables analyses as per the intention-to-treat principle by assuming dropouts from assessment to be non-responders (14, 15).

Data analyses

Our primary comparison of interest was between the fixed dose regimen at the lowest of each drug's licensed dose range and the flexible dose regimen which allows upward titration going above that lowest dose while side effects permitted.

We first calculated summary odds ratios of each drug over placebo among the fixed dose regimen studies (OR_{Fixed}) and those of the flexible dose regimen studies (OR_{Flex}). We then calculated the ratio of the two ORs ($ROR= OR_{Flex} / OR_{Fixed}$) for the same drug. The ROR can be interpreted as the indirect OR between the flexible and fixed dosing of the same drug, with an ROR>1 indicating superiority of the flexible regimen over the fixed one. The five drug-specific RORs for the SSRIs were then further meta-analysed to obtain a summary ROR for the SSRIs; RORs for venlafaxine and mirtazapine were reported separately. In the case of multi-arm studies which contributed to two or more of the above comparisons (e.g. a study comparing fixed doses of two different drugs versus placebo, or a study comparing fixed and flexible doses of the same drug versus placebo), we divided the number of participants in the placebo arm appropriately to avoid double-counting them in the summary ORs or RORs (11). The random effects model was used for all the meta-analyses and heterogeneity was measured using I^2 and the heterogeneity variance.

We applied the same analytical strategies to the dichotomous secondary outcomes. For the continuous secondary outcome of depression severity, we calculated the standardised mean difference (SMD) and the difference in SMDs ($DSMD= SMD_{Flex} – SMD_{Fixed}$), with an SMD<0 indicating greater reduction in severity of the flexible regimen over the fixed one.

Sensitivity analyses

Upward titration beyond 40 mg fluoxetine equivalents could be disadvantageous against the flexible regimen, because our previous analyses suggested a dose-response curve of SSRIs and mirtazapine that is possibly decreasing above 40 mg fluoxetine equivalents (3). In this dose-response meta-analysis of SSRIs, the following doses were considered equivalent to fluoxetine 20 mg: citalopram 20 mg, escitalopram 9 mg, paroxetine 17 mg, and sertraline 49 mg. We therefore ran a sensitivity analysis limiting the flexible regimens to those that allowed titration only up to double the minimum licenced dosage (corresponding roughly with 40 mg fluoxetine equivalents).

We also ran an additional sensitivity analysis in which we compared the flexible dose studies that allowed dose ranges below the minimum licensed dose against the fixed minimum licensed dose studies.

As the comparison of the effects of interventions between fixed and flexible dosing are not randomised i.e. participants were randomised within studies but not across studies, confounding is possible. We therefore examined the comparability of studies in study year, number of participants per study, average age of participants, proportion of women enrolled, baseline depression severity, or length of trial. If differences in variables were noted, we calculated adjusted ORs via meta-regression and re-calculated the RORs.

We conducted all analyses in R (version 3.6.1) using the *meta* package (version 4.9-6). The data and the analysis scripts that generated results and figures can be found in GitHub (https://github.com/esm-ispm-unibe-ch-REPRODUCIBLE/Reproduce_Fixed_low_dose_vs_flexible_dose).

RESULTS

Characteristics of the included studies

We have included 123 RCTs (29,420 participants), which contributed 66 comparisons between minimum dose fixed regimens and placebo and 76 comparisons between flexible dose regimens and placebo (eFigure 1 in Appendix 1). We had obtained unpublished information for 78 of the 122 RCTs (63.9 %). Table 1 shows the demographic, clinical and other characteristics of the included studies by regimen and drug. The participants were typically in their 40s, predominantly women and scored slightly above 20 on the 17-item HAMD at baseline on average. The trials lasted around 8 weeks.

Primary outcome: response of SSRIs, venlafaxine and mirtazapine

Figure 1 shows the RORs of response in the flexible dose studies over the fixed dose studies for three subgroups of SSRIs, venlafaxine and mirtazapine. Moderate heterogeneity was observed in the meta-analysis of RORs of SSRIs (I-squared=59.3%, 95% confidence interval (CI): 0% to 84.8%, heterogeneity variance τ^2= 0.024). There were no important differences between the flexible and fixed dosing for SSRIs (ROR 0.96, 95%CI: 0.73 to 1.25). Similarly, the results for venlafaxine (ROR 1.24, 0.96 to 1.60) and mirtazapine (ROR 0.77, 0.33 to 1.78)

were uncertain with wide confidence intervals. Appendix 4 shows the individual study ORs for response, synthesized by drug and regimen (eFigures 2-5).

Secondary outcomes: depression severity, dropouts due to side effects, dropouts for any reason

Figure 2a shows the DSMD of depression severity; 2b RORs of dropouts due to side effects; 2c RORs of dropouts for any reason, respectively. There were no important differences between the flexible and the fixed regimens in any of the comparisons. Evidence for venlafaxine and, in particular, mirtazapine was imprecise. Flexible dosing of SSRIs might even be associated with more dropouts due to adverse events compared to fixed dosing (Figure 2b).

Sensitivity analyses

Figure 3 compares flexible regimens that titrate only up to 40 mg fluoxetine equivalents versus fixed dose. The point estimates of RORs were broadly similar to those in Figure 1; however, the ROR for venlafaxine was 1.30 (1.02 to 1.65), in favour of the flexible dosing between 75-150 mg of venlafaxine over the fixed dosing staying at 75 mg.

Flexible dose studies starting below the minimum licensed dose were available only for citalopram, paroxetine and mirtazapine. The confidence intervals were wide and there was no evidence that flexible dosing allowing doses lower than the minimum licensed dose was any more or less efficacious than the fixed minimum licensed dose (Appendix 5, eFigure 5).

Examination of Table 1 suggested that fixed dose studies tended to be more recent and larger than flexible dose studies for all drugs. In a logistic regression model, the study year was significantly associated with the dosing regimen when the drug was controlled for ($p=0.01$) but not the average sample size per study ($p=0.07$). Appendix 5, eFigure 6 shows the results for SSRIs scaling the RORs to year 2000 via meta-regression on the study year. The ROR was essentially unchanged at 0.97 (0.77 to 1.24) but heterogeneity was reduced (the heterogeneity variance was reduced by 32%).

DISCUSSION

The study aimed to examine whether the flexible upward titration of antidepressants beyond their minimum licensed dose conferred any benefit above the fixed dosing at the minimum dose in the acute phase treatment of major depression. RORs of response between the flexible dose regimen going above the minimum licensed dose and the fixed dose regimen staying at the minimum dose did not show any advantage of the flexible dosing for SSRIs,

venlafaxine or mirtazapine. The lack of evidence for difference in efficacy was confirmed when the regimens were compared in terms of depression severity. We could not detect any important differences in terms of tolerability and acceptability between the two regimens either. However, imprecision in the summary effects was considerable in some of these outcomes.

In the literature the advantage of flexible or fixed dose regimens had been discussed from the viewpoint of clinical trial design. An earlier report found that flexible dose studies were more often able to detect statistically significant drug-placebo differences than fixed dose studies (16). More recent reports, however, have not found such a difference between the two types of clinical studies (17, 18). Our results are in line with these more recent reports.

We are aware of only one RCT that compared flexible dosing up to the minimum of licensed dosage versus flexible dosing up to double that dosage. It was a large-scale pragmatic trial comparing the initial strategy of titrating up to 50 mg versus 100 mg of sertraline if side effects permitted. Altogether 970 participants were allocated to the 50 mg/day and 1,041 to the 100 mg/day arms, but there was no statistically significant difference in terms of depression severity or burden of side effects between the two groups after nine weeks of treatment (19).

Our previous dose-response meta-analyses of the fixed dose studies suggested no increase in response going beyond 40 mg of fluoxetine equivalents for SSRIs or mirtazapine and limited increase in response for venlafaxine, but steeply increased dropouts due to side effects for all the agents (3). When we compare the current findings including flexible dose studies with these results based on fixed dose studies, flexible dosing was able to mitigate but not decrease the harms of the higher doses and was unable to boost efficacy. The higher efficacy beyond 75 mg for venlafaxine may be considered to be in line with our previous meta-analysis, which suggested initially increasing efficacy up to around 75-150 mg, followed by a more modest increase thereafter.

In our previous report we suggested that these findings were consistent with the observation from PET studies that substantial (80%) blockade of the serotonin transporter occurs with minimum therapeutic doses of SSRIs and only small increases in occupancy become apparent with further dose escalation (20). A similar finding obtains with venlafaxine but the ability of venlafaxine to inhibit noradrenaline reupake at higher doses may account for its improved efficacy within a somewhat wider dose range (21).

Our results of no additional benefits from initial flexible dosing strategy going beyond the low dosage are also in line with those from dose escalation strategies as the second line treatment after initial treatment failure. RCTs and their meta-analysis have repeatedly found that non-response to the initial minimum dose does not justify dose escalation beyond the initial dose: for example, among non-responders to initial 20 mg of fluoxetine equivalents, increasing the dosage to 40 mg or 60 mg was not more efficacious than, and only as tolerated as, staying at 20 mg (22-25). A particularly well-designed study provides a neurobiological explanation that is consonant with the observations cited above: in this study patients with major depression who had not responded to 20 mg of paroxetine were randomized to further paroxetine increase to 30-50 mg or to addition of placebo: after six weeks, dose escalation neither increased serotonin transporter occupancy nor decreased depressive severity in comparison with continuing 20 mg of paroxetine (26).

The current analyses are not without some weaknesses. First, RORs are essentially indirect comparisons between the flexible dose regimen arms versus the fixed dose regimen arms via placebo arms. The estimates can then be confounded when effect modifiers are unevenly distributed between the comparisons involving the flexible dose arms and those involving the fixed dose arms. The fixed dose studies tended to be more recent and larger than flexible dose studies. This finding is consistent with our previous observation that recent trials of antidepressants are employing the fixed dose regimen more frequently (27). Moreover, the study year has been suggested to be a surrogate marker for study quality and other secular changes in the trial characteristics (28). Adjusting for the study year reduced heterogeneity, as expected, but findings were in line with the overall results. Second, the current study is based on study-level summary statistics and we were unable to identify subgroups of patients who would potentially need upward or downward titration. We would need individual patient data to elucidate such subgroup differences. Clinically, however, this may be less of a problem because it is natural to adjust the dosages according to the individual patient's characteristics such as body weight, past experiences with similar drugs, comorbidity including liver or renal functions, or age: the current study only recommends that the average of such upward or downward adjustments be around the minimum of the licensed range. Third, although we were able to include 122 studies representing 32,373 participants, the confidence intervals around the pooled estimates were not always precise. The ROR of response for SSRIs was 0.96 (0.73 to 1.25), which would translate into a risk difference of -1% (-7% to 5%) for an assumed response rate of 35% (3). If we consider 5% risk

difference in response to be the smallest worthwhile difference between two treatment regimens, the estimated confidence interval rules out the possibility of superiority of the flexible regimen over the fixed regimen. However, the confidence intervals were much wider for venlafaxine and mirtazapine. Fourth, most of the included studies were company-sponsored phase II or III studies. As such, the focus of flexible titration may have been related more to tolerability or safety rather than efficacy. Also we do not have information about how fine-grained flexible dosing was in each study. There remains some possibility that flexible titration targeting at efficacy and conducted at smaller steps than was actually undertaken in the included studies might increase efficacy and/or tolerability. This remains an empirical question to be tested out. Lastly, the search date for this review could be considered old: however, an update search for eligible studies in PubMed in March 2019 revealed no additional study.

The evidence about the dose-response relationship based on fixed dose studies (3), the evidence from dose escalation studies after non-response (22-25), the biological findings for transporter occupancy (20, 26), results from the megatrial directly comparing two doses (19), and our present comparison of the fixed versus flexible regimens, all converge to suggest that there is no added benefit going beyond the minimum dose for SSRIs and mirtazapine. Venlafaxine may be beneficially and harmlessly increased between 75-150 mg. Considering also the cost of increasing the dose, the present study suggests that we should no longer, speculatively without due evidence, advocate the policy of increasing the dosage above the minimum licensed dose of SSRIs and mirtazapine, until further evidence to the contrary becomes available.

Conflicts of interest

TAF has received lecture fees from Mitsubishi-Tanabe, MSD and Shionogi. He has received research support from Mitsubishi-Tanabe. He has a patent 2018-177688 pending. SL has received honoraria for consulting or lectures from LB Pharma, Otsuka, Lundbeck, Boehringer Ingelheim, LTS Lohmann, Janssen, Johnson & Johnson, TEVA, MSD, Sandoz, SanofiAventis, Angelini, Recordati, Sunovion, and Geodon Richter. GS has received fees paid to the University of Bern for participating in a meeting as real-world evidence and meta-analysis expert from Biogen and Merck. No other disclosures were reported.

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Data availability statement

All the data and the analysis scripts that generated results and figures can be found in GitHub (https://github.com/esm-ispm-unibe-ch-REPRODUCIBLE/Reproduce_Fixed_low_dose_vs_flexible_dose).

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Table 1. Characteristics of the included studies

Drug	Dosing regimen	No of comparisons	Median year of study completion (range)	Mean sample size	Mean age	Proportion of women (%)	Baseline HAMD17 (no of studies)	Mean length of trial (weeks)	Dosage		
									Minimum	Maximum	Average
citalopram	fixed	7	2001 (1992-2006)	178.6	41.9	60	23.7 (1)	6.0	-	-	20
	flexible	4	2000 (1999-2000)	192.9	41.7	-	-	7.0	20	80	54.5
escitalopram	fixed	9	2007 (2000-2011)	289.8	44.0	67	21.1 (3)	8.0	-	-	10
	flexible	10	2004 (2000-2009)	241.9	42.4	54	21.9 (2)	8.4	10	20	13.0
fluoxetine	fixed	21	2001 (1987-2013)	150.7	42.3	64	22.3 (7)	7.3	-	-	20
	flexible	13	1999 (1985-2007)	241.6	42.9	63	-	8.3	20	80	44.3
paroxetine	fixed	17	2003 (1992-2009)	227.1	42.9	67	23.8 (11)	7.6	-	-	20

	flexible	19	1997 (1986-2011)	227.8	40.1	58	23.4 (5)	8.8	20	60	31.0
sertraline	flexible	4	2004 (1995-2012)	91.3	40.4	47	-	6.0	-	-	50
	fixed	16	2000 (1990-2013)	222.9	42.5	62	21.3 (11)	8.0	50	200	108.9
mirtazapine	fixed	3	1998 (1990-2009)	113.3	39.7	65	22.5 (1)	6.7	-	-	15
	flexible	1	-	117.0	46.0	53	-	6.0	15	50	33.0
venlafaxine	fixed	5	1998 (1998-2011)	181.3	40.2	58	-	7.2	-	-	75
	flexible	13	1999 (1994-2011)	210.1	43.6	62	-	7.7	75	225	141.1

Figure 1. RORs of response of the flexible dose starting from the minimum licensed dose and titrating upward, over the fixed minimum licensed dose

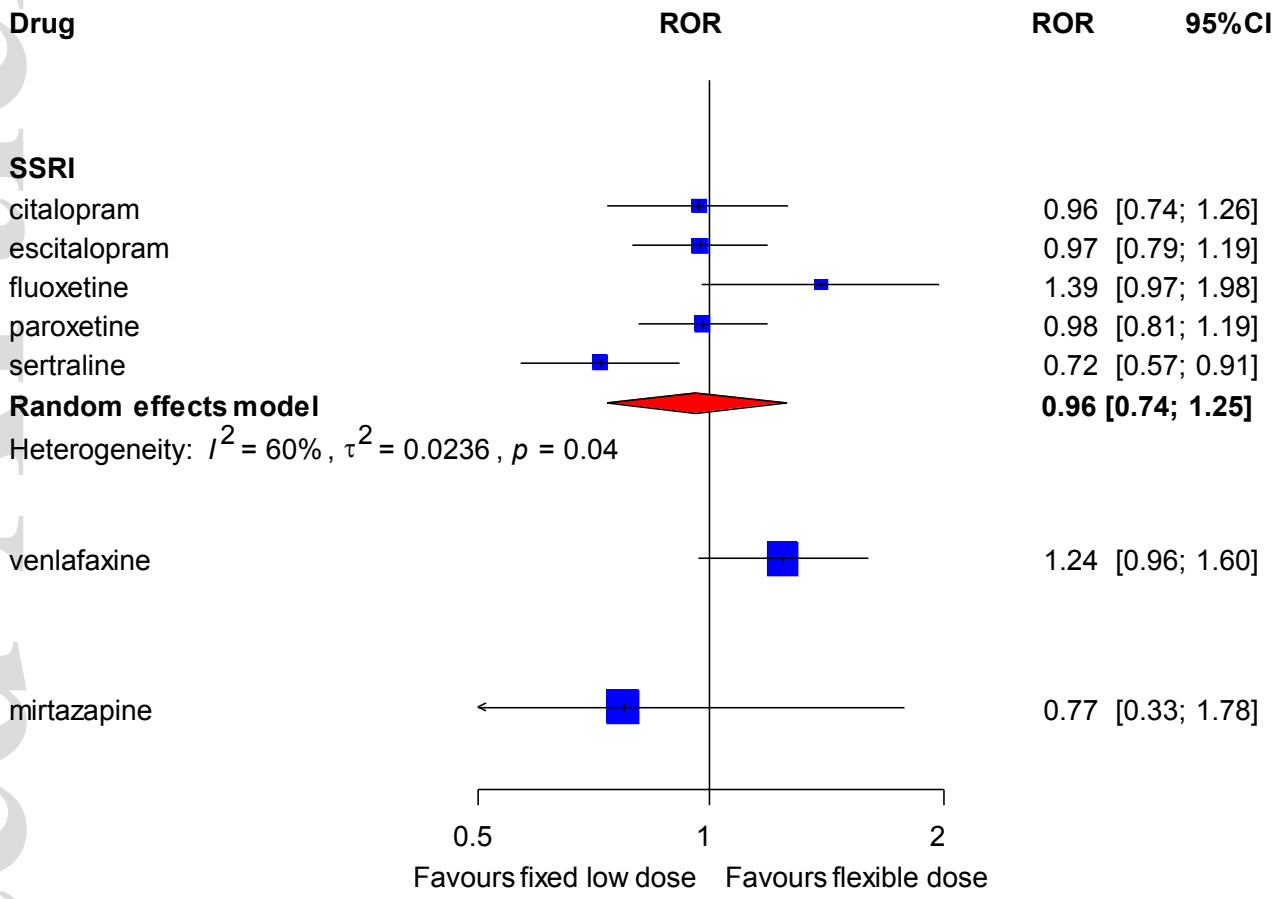
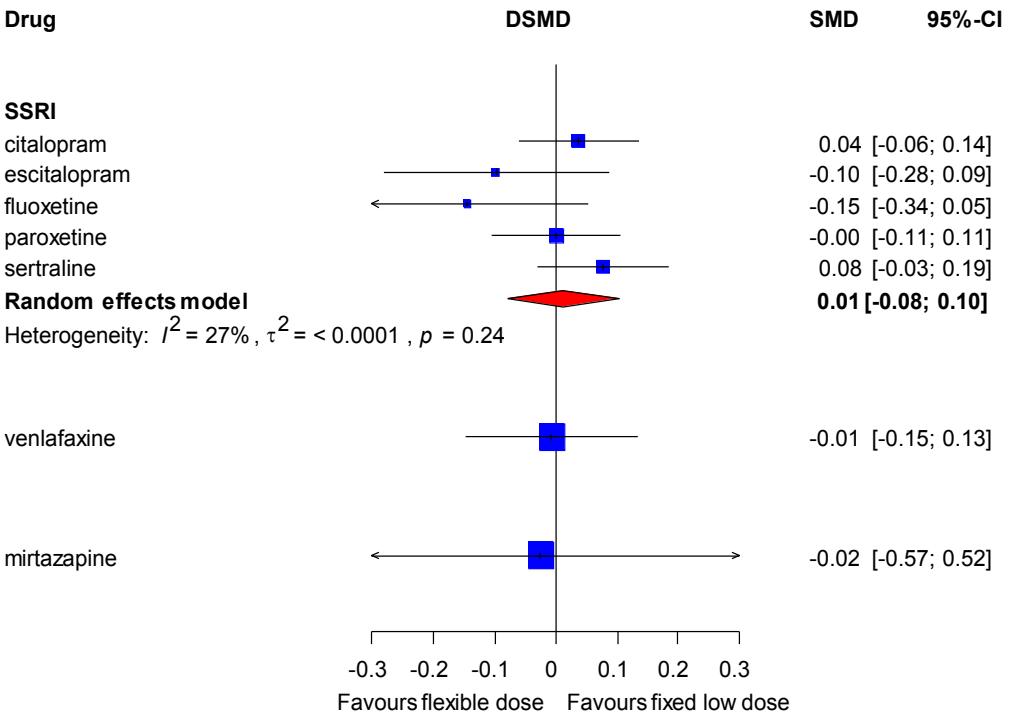
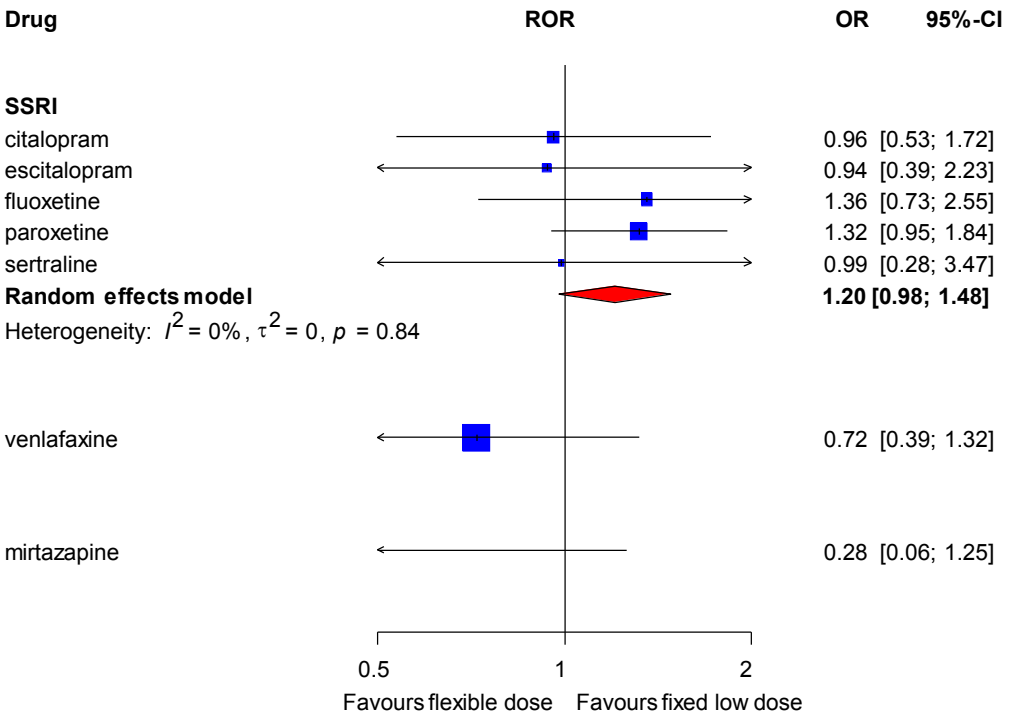


Figure 2. DSMDs of depression severity, RORs of dropouts due to side effects, RORs of dropouts for any reason

2a. DSMDs of depression severity of the flexible dose starting from the minimum licensed dose and titrating upward, over the fixed minimum licensed dose



2b. RORs of dropouts due to side effects of the flexible dose starting from the minimum licensed dose and titrating upward, over the fixed minimum licensed dose



2c. RORs of dropouts for any reason of the flexible dose starting from the minimum licensed dose and titrating upward, over the fixed minimum licensed dose

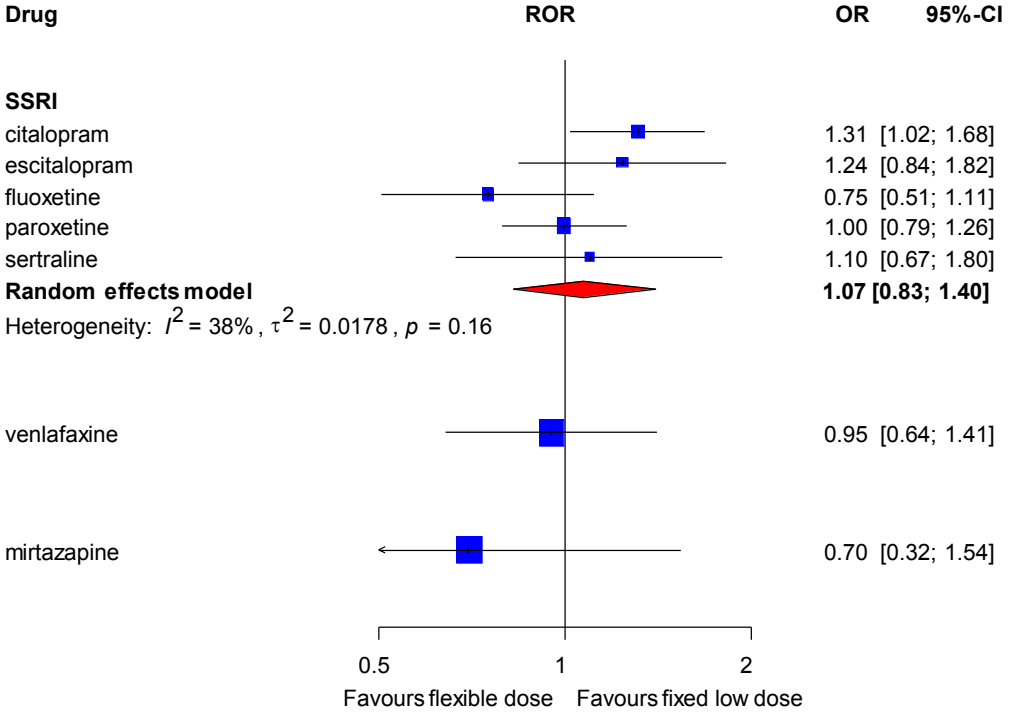


Figure 3. Sensitivity analysis: RORs of response of the flexible dose starting from the minimum licensed dose and titrating upward to double that dose, over the fixed minimum licensed dose