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Optimal doses of antidepressants in dependence on age: Combined covariate actions in Bayesian network meta-analysis

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ABSTRACT

Background: The meta-analysis by Furukawa et al. (The Lancet Psychiatry 2019, 6(7)) reported optimal doses for antidepressants in adult major depressive disorder (MDD). The present reanalysis aimed to adjust optimal doses in dependence on age. *Methods:* Analysis was based on the same dataset by Cipriani et al. (The Lancet 2018, 391(10128)) comparing 21 antidepressants in MDD. Random-effects Bayesian network meta-analysis was implemented to estimate the combined covariate action using restricted cubic splines (RCS). Balanced treatment recommendations were derived for the outcomes efficacy (response), acceptability (dropouts for any reason), and tolerability (dropouts due to adverse events). *Findings:* The combined covariate action of dose and age suggested agomelatine and escitalopram as the best-balanced antidepressants in terms of efficacy and tolerability that may be escalated until 40 and 60 mg/day fluoxetine equivalents (mg/day$_{FE}$), respectively, for ages 30–65 years. Desvenlafaxine, duloxetine, fluoxetine, milnacipran, and vortioxetine may be escalated until 20–40 mg/day$_{FE}$, whereas bupropion, citalopram, mirtazapine, paroxetine, and venlafaxine may not be given in doses $>$ 20 mg/day$_{FE}$. Amitriptyline, clomipramine, fluvoxamine, levomilnacipran, reboxetine, sertraline, and trazodone revealed no relevant balanced benefits and may therefore not be recommended for antidepressant treatment. None of the antidepressants was observed to provide balanced benefits in patients >70 years because of adverse events exceeding efficacy. *Interpretation:* Findings suggest that the combined covariate action of dose and age provides a better basis for judging antidepressant clinical benefits than considering dose or age separately, and may thus inform decision makers to accurately guide antidepressant dosing recommendations in MDD. *Funding:* No funding.

1. Introduction

The recent meta-analysis by Furukawa et al. [1] reported optimal doses for the use of antidepressants in the acute-phase treatment of adult major depressive disorder (MDD). Results showed a moderate dose-dependent increase in efficacy (response rate) until 40 mg/day fluoxetine equivalents (mg/day$_{FE}$) associated with an exponential decrease in tolerability (dropouts due to adverse effects) up to 80 mg/day$_{FE}$ [2,3]. The current recommendation is therefore that the lower range (20–40 mg/day$_{FE}$) of the licensed dose (20–80 mg/day$_{FE}$) probably achieves an optimal balance between efficacy and tolerability for the majority of patients receiving antidepressants in MDD [1]. The meta-analysis by Furukawa et al. [1] however did not adjust dosing for age, another important demographical covariate in antidepressant treatment [4–10]. Antidepressant use in the elderly ($>$ 60 years) is associated with an increased risk of potentially clinical significant adverse events (AEs). Common AEs affect the cardiovascular system (e.g., orthostatic hypotension, QTc interval prolongation), metabolic system (e.g., weight gain, hyponatremia), the central nervous system (extrapyramidal symptoms), and are associated with osteoporosis, falls and fractures [11–13]. The increased risk of AEs might in part be due to dosing not taking into account known age-related changes in antidepressant pharmacokinetics and/or drug-drug interactions (DDIs) [14–16]. DDIs are more common in the elderly due to the prescription of multiple medications under comorbid conditions [17]. Indeed, antidepressant prescribing in older adults has recently been reported to be pharmacokinetically inappropriate in 77% (underuse) and 42% (overuse) [18], with a subset of patients experiencing pharmacodynamic tolerance after long-term treatment [19]. Antidepressant use is also associated with higher suicidality [20], particularly in elderly men (completed suicides) [21,22] but also in patients $<$ 25 years (not completed suicides) [23]; with the latter also having a higher risk of hyperarousal events in response to antidepressants [24]. Together, age is an important consideration for whether, when, and how to treat a patient with antidepressants throughout the life cycle, and with what potential risk versus benefit. It therefore seems sensible to adjust antidepressant treatment recommendations for both dose and age to optimally meet the needs of

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individual age-groups. The present reanalysis therefore asked whether antidepressant dosing recommendations reported by Furukawa et al. [1] would change in dependence on age.

The present analysis made use of the same dataset assessed by Furukawa et al. [1], the GRISELDA dataset provided by Cipriani et al. [25]. which compares 21 antidepressants in adult MDD based on 522 randomized controlled trials (RCTs). Furukawa et al. [1] selected 77 fixed dose trials and collapsed antidepressants based on their mechanisms of actions [26] across selective serotonin reuptake inhibitors (SSRIs) with separate analyses for mirtazapine and venlafaxine. Earlier meta-analyses also focused on SSRIs [1,27,28] or a limited number of antidepressants (citalopram, paroxetine, sertraline) [29]. Clustering analysis into class-based approaches may increase the evidence base and precision of effect estimates, but the direct interpretation of individual antidepressants is lost, which makes clinical decision making difficult. The present analysis therefore aimed to evaluate optimal dosing for all 21 individual antidepressants available.

To account for potential nonlinearity of dose phenomena, Furukawa et al. [1] fitted a nonlinear model using restricted cubic splines (RCS) [30] as implemented in the dosresmeta package [31]. This approach allows for convenient and robust multivariate dose-response meta-analysis from aggregated data using flexible non-linear models. The method is, however, not based on the Bayesian framework, which is still considered the gold standard for network meta-analysis (NMA) [32]. The present analysis therefore aimed to implement a nonlinear model based on RCS into Bayesian NMA. The implementation further aimed to adjust not only for separate covariates (i.e., dose or age) but also for the combined covariate action. The methodological approach presented here thus provides the first example how nonlinear combined covariate effects can be analyzed and graphically presented based on Bayesian NMA. The results are expected to support clinical decision making in defining optimal dosages for antidepressant treatment in patient populations differing in age.

2. Methods

2.1. Statistical analysis

2.1.1. Bayesian models for NMA

Based on standard Bayesian random-effects NMA [32], a model based on restricted cubic splines (RCS) was implemented to assess nonlinear treatment-by-covariate interactions with two continuous covariates (x_a/x_b, i.e., dose and age). The spline basis matrices for the main covariate effects were generated using the function rcs and those for the interaction effects, i.e., the tensor product splines, were generated using the restricted interaction operator %ia%, both implemented in the rms package [33]. Interaction effects were restricted to be not doubly nonlinear with products involving nonlinear effects on both covariates not included in the model. The RCS model was assessed using 3 knots based on combinations out of 7 possible knot locations for each covariate (dose (mg/day$_{FE}$) = [10, 20, 30, 40, 50, 60, 70]; age (years) = [35, 40, 45, 50, 55, 60, 70]), resulting in N = 35 models per covariate. This allowed for a more extensive selection of the optimal knot location compared to Furukawa et al. [1], who evaluated only 8 different knot combinations. The full model contained regression coefficients for the main covariate effects ($B_{1a,b}$, $B_{2a,b}$ corresponding to the linear and nonlinear main effect components) and the interaction effects (B_3, B_4, B_5 corresponding to the linear and nonlinear interaction effect components).

Covariates were centered and standardized by subtracting the mean ($\bar{x}$) and dividing by the standard deviation (SD, σ). Standardization facilitates the interpretation of beta estimates derived from covariates with different units for direct comparison of their contribution in determining the outcomes. Missing covariate data were given informative priors normally distributed $x_i \sim N(\bar{x}, \sigma^2)$ common across trials, an imputation technique assuming covariate data to be missing at random.

Treatment-by-covariate interactions were assumed to be exchangeable-related drawn from a random distribution with common mean (B) and between-treatment variance (σ_B^2) [32].

Modeling was conducted using the JAGS software (version 4·3·0) [34]. Simulations were run for 3 chains with an adaptive phase of 100,000, a burn-in of 100,000, and a sampling phase of 200,000 iterations, thinned such that every 50th iteration was retained. Effect sizes on the log odds ratio (LOR) scale were estimated at 10 equally spaced covariate values (Fig. S2). Convergence was ensured by considering the Brooks–Gelman–Rubin diagnostics [35] with the potential scale reduction factor $\overline{R} \leq 1.05$ accepted as implying convergence [36]. Bayesian model selection of the best-fitting RCS model was based on the deviance information criterion (DIC), a measure of goodness-of-fit and complexity [36]. The supplementary appendix provides details on the code used to conduct the analysis.

2.1.2. Balanced treatment recommendations

Since clinical decisions are made not only based on efficacy or tolerability separately, but also by considering the best mixture between outcomes, balanced benefits were assessed for each antidepressant. For this purpose, the relative treatment effects between two outcomes were mapped onto the octants of the two-dimensional coordinate system (Fig. S6). Balance mapping was defined with the balanced log odds ratio (LOR$_B$) scale representing the balance between the relative treatment effects of efficacy (x, mapped on the x-axis) versus tolerability (y, mapped on the y-axis) compared to placebo (zero). This was calculated as a function of covariate values along the dose (i) and age (j) dimensions, with $\mathrm{LOR}_B(i,j) = x(i,j) - y(i,j)$ for mapping on the 1st–4th octant and $\mathrm{LOR}_B(i,j) = x(i,j)$ for mapping on the 5th–8th octant. Balanced benefits were assumed if the balance on the LOR$_B$ scale was in favor of efficacy, i.e., if the balance was mapped onto the 1st, 7th, or 8th octant. In order to avoid balanced treatment recommendations being driven by implausible interferences based on potential extrapolation in NMA results [37], recommendations were constrained to the actual dose ranges of individual antidepressants available in the data. The supplementary appendix provides details on the definition of the balanced dose recommendations.

2.2. GRISELDA dataset

The GRISELDA dataset [38] provided by Cipriani et al. [25] comprises 522 RCTs (total of 116,477 patients) conducted between 1979 and 2016. The dataset compares 21 antidepressants, agomelatine (AGO), amitriptyline (AMI), bupropion (BUP), citalopram (CIT), clomipramine (CLO), desvenlafaxine (DES), duloxetine (DUL), escitalopram (ESC), fluoxetine (FLO), fluvoxamine (FLV), levomilnacipran (LEV), milnacipran (MIL), mirtazapine (MIR), nefazodone (NEF), paroxetine (PAR), reboxetine (REB), sertraline (SER), trazodone (TRA), venlafaxine (VEN), vilazodone (VIL), and vortioxetine (VOR), together forming a network of N = 101 treatment-by-treatment comparisons (Fig. S1). Information on age (mean 44·3 ± 8·8, range 30–80 years) was available in 451 (86%) trials comprising 105,469 patients. Information on dose (mean 30·4 ± 14·6, range 5–80 mg/day$_{FE}$) was available in 497 (95%) trials comprising 110,641 patients (placebo arms not shown in plot). Doses were converted to 20 mg/day fluoxetine equivalents (mg/day$_{FE}$) using the conversion by Hayasaka et al. [2], supplemented by the daily defined dose (DDD) method [3]. Only vilazodone had no defined equivalent and is therefore only reported in the supplementary appendix. The analysis included 48 (9%) trials with dosages outside the licensed ranges

approved by the regulatory agencies in the USA and Europe (Table S1 and Fig. S2).

The primary analysis included 188 fixed dose trials, results of which are reported in the main text. Nefazodone had no fixed dose trials and was therefore not included in the primary analysis. The secondary analysis included 499 trials with both fixed and flexible doses (based on mean flexible ranges), results of which are reported in the supplementary appendix. The inclusion of flexible dose trials has been criticized because of the inevitable confounding between response and dose for individual patients and hence the likelihood of the aggregated data being uninformative regarding the actual doses given [39,40].

Primary outcomes were efficacy in terms of response rate ($\geq$ 50% reduction on the Hamilton Depression Rating Scale, HDRS-17) [41], acceptability (dropout rate for any reason, $dropout_{ANY}$), and tolerability (dropout rate due to adverse events, $dropout_{AE}$). Secondary outcome was remission rate ($<$ 7 or $<$ 8 on the HDRS-17 score), results of which are reported in the Supplementary Appendix.

3. Results

3.1. Bayesian model selection

Best-fitting RCS model were selected based on the smallest DIC (Table S2). Covariate dose fitted best with knots located at [10, 20, 40] mg/day_{FE}; these knots are located at areas with greater covariate density (Fig. S2) compared to those reported by Furukawa et al. [1] ([10, 20, 50] mg/day_{FE}), and may therefore reflect dose phenomena better. Covariate age was best described with knots located at [40, 45, 60] years; these knots are reasonable because of the relatively large contribution of the upper end of the age spectrum to treatment effects (Fig. S3) [37].

3.2. Combined covariate action

The combined covariate action of $dose_{RCS}$ & age_{RCS} based on the best-fitting RCS models reduced between-trial heterogeneity (σ) by 29% (efficacy), 51% (acceptability), and 59% (tolerability) relative to the unadjusted model (Fig. S4). Heterogeneity was low for efficacy (σ = 0.026) and acceptability (σ = 0.018), and moderate for tolerability (σ = 0.061) [42]. Maximum effect sizes were medium for efficacy (LOR 0.61, d = 0.34), acceptability (LOR 0.25, d = 0.14), and tolerability (LOR 1.02, d = 0.56) compared to Cohen's d [43]. For brevity, the combined covariate action is illustrated across all antidepressants (Table 1 and Fig. 1), while details on individual antidepressants can be found in the supplementary appendix (Table. S3 and Fig. S5−S7).

Dose adjustment revealed no significant effects on efficacy and acceptability, but significantly affected tolerability (Table 1). Particularly, main effects of dose suggested a nonsignificant linear increase in efficacy with increasing dose. Efficacy was best described as weak linear increasing curves, without decreasing trends as reported by Furukawa et al. [1] Acceptability ($dropout_{ANY}$) was unaffected reflected by flat curves. By contrast, tolerability ($dropout_{AE}$) was suggested to strongly linearly decrease with increasing dose in all antidepressants (fixed dose trials: linear common B = 0.66, 95% CrI [0.21−1.08]; fixed and flexible dose trials: linear common B = 0.61, 95% CrI [0.19−1.03]). Tolerability was best described by steep linear-plateau curves, which settled approximately at 20 mg/day_{FE} after which curves increased flatter until 80 mg/day_{FE}, compared to the more exponential curve reported by Furukawa et al. [1] Estimates of the decrease in tolerability were found to be more than double the size of the increase in efficacy, in line with Furukawa et al. [1].

Age adjustment revealed no significant effects on efficacy, but affected both acceptability and tolerability (Table 1). In particular, main effects of age suggested a nonsignificant nonlinearly decrease in response with increasing age. Acceptability ($dropout_{ANY}$) significantly decreased with increasing age (fixed dose trials: nonlinear common B = 0.18, 95% CrI [−0.05−0.42]; fixed and flexible dose trials: nonlinear common B = 0.21, 95% CrI [0.02−0.40]). Likewise dose-adjustment, the strongest effect was observed on tolerability ($dropout_{AE}$) which nonlinearly decreased with from approximately $>$ 60 years upwards in most antidepressants (fixed dose trials: nonlinear common B = 0.53, 95% CrI [0.10−1.14]; fixed and flexible dose trials: nonlinear common B = 0.40, 95% CrI [0.12−0.69]).

The dominant effects on tolerability ($dropout_{AE}$) were supported by a significant interaction effect between the linear $dose_{RCS}$ × nonlinear age_{RCS} components (fixed dose trials: common B = −1.43, 95% CrI [−3.08−0.26]; fixed and flexible dose trials: common B = −0.34, 95% CrI [−0.90−0.23]), suggesting increasing dropouts due to adverse events with increasing dose and increasing age (Table 1). The remaining

Table 1
Adjusted beta estimates. Standardized common beta estimates (B) adjusted for the combined covariate action of $dose_{RCS}$ & age_{RCS} and their interaction based on the best-fitting RCS models in fixed dose trials. Listed are the linear and nonlinear main effect components of $dose_{RCS}$ and age_{RCS} ($B_{1a,b}$, $B_{2a,b}$), and the linear and nonlinear interaction effect components between $dose_{RCS}$ × age_{RCS} (B_3, B_4, B_5). Statistical significant betas (95% CrI excluding zero) are highlighted (*). See Table S3 for details on individual antidepressants.

	Fixed dose			Fixed and flexible dose		
Dose	B_{1a} (95% CrI) Linear	B_{2a} (95% CrI) Nonlinear		B_{1b} (95% CrI) Linear	B_{2b} (95% CrI) Nonlinear	
Response	0.11 (−0.18−0.44)	−0.03 (−0.43−0.34)		0.09 (−0.11−0.30)	−0.01 (−0.26−0.24)	
Remission	0.19 (−0.12−0.51)	−0.07 (−0.48−0.33)		0.13 (−0.11−0.36)	−0.06 (−0.34−0.24)	
$Dropout_{ANY}$	0.29 (−0.04−0.67)	−0.27 (−0.73−0.14)		0.24 (−0.04−0.48)	−0.24 (−0.52−0.06)	
$Dropout_{AE}$	0.66 (0.21−1.08)*	−0.48 (−0.99-0.09)		0.61 (0.19−1.03)*	−0.44 (−0.93−0.05)	
Age	B_{1a} (95% CrI) Linear	B_{2a} (95% CrI) Nonlinear		B_{1b} (95% CrI) Linear	B_{2b} (95% CrI) Nonlinear	
Response	0.03 (−0.08−0.14)	−0.11 (−0.41−0.18)		0.02 (−0.08−0.13)	−0.12 (−0.29−0.05)	
Remission	0.04 (−0.07−0.16)	−0.16 (−0.43−0.06)		−0.01 (−0.12−0.09)	−0.16 (−0.34−0.02)	
$Dropout_{ANY}$	−0.09 (−0.19−0.01)	0.18 (−0.05−0.42)		−0.08 (-0.20−0.03)	0.21 (0.02−0.40)*	
$Dropout_{AE}$	−0.09 (−0.32−0.14)	0.53 (0.10−1.14)*		−0.09 (−0.27−0.09)	0.40 (0.12−0.69)*	
Dose × Age	B_3 (95% CrI)	B_4 (95% CrI)	B_5 (95% CrI)	B_3 (95% CrI)	B_4 (95% CrI)	B_5 (95% CrI)
	Dose linear × Age linear	Dose nonlinear × Age linear	Dose linear × Age nonlinear	Dose linear × Age linear	Dose nonlinear × Age linear	Dose linear × Age nonlinear
Response	0.12 (−0.29−0.55)	−0.19 (−0.70−0.31)	−0.06 (−0.60−0.41)	−0.02 (−0.28−0.26)	0.07 (−0.25−0.38)	−0.03 (−0.29−0.24)
Remission	0.05 (−0.26−0.34)	0.05 (−0.37−0.45)	−0.09 (−0.38−0.20)	−0.20 (−0.50−0.08)	0.27 (−0.05−0.61)	0.12 (−0.18−0.41)
$Dropout_{ANY}$	−0.04 (−0.44−0.42)	0.09 (−0.48−0.63)	−0.02 (−0.29−0.24)	−0.07 (−0.59−0.36)	0.03 (−0.45−0.59)	0.04 (−0.37−0.52)
$Dropout_{AE}$	0.43 (−0.06−0.92)	−0.45 (−1.04−0.15)	−1.43 (−3.08−0.26)*	0.37 (−0.29−0.96)	−0.44 (−1.09−0.27)	−0.34 (−0.90−0.23)

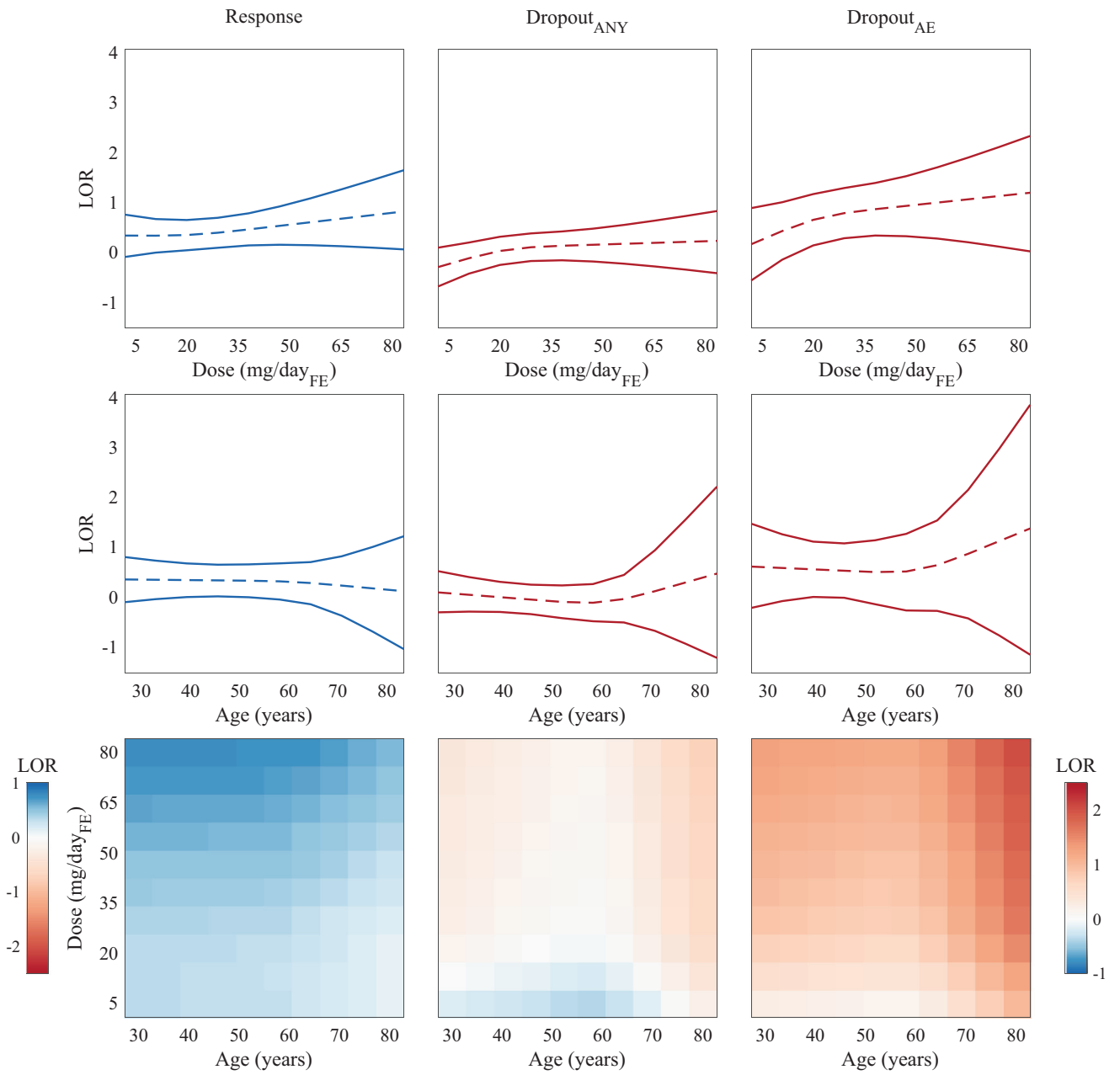

Fig. 1. *Covariate adjusted meta-regression plots.* Antidepressant effects relative to placebo illustrated for the main effects of (*Top*) dose$_{RCS}$, (*Middle*) age$_{RCS}$, and (*Bottom*) the combined covariate action of dose$_{RCS}$ & age$_{RCS}$ in fixed dose trials. Values greater 0 on the log odds ratio (LOR) scale indicate increase in response/remission or increase in dropout$_{ANY/AE}$ compared to placebo. Plots illustrate the averaged effect sizes across all antidepressants; see Fig. S5 for individual antidepressants.

interaction effects were not significant suggesting that dose and age act as independent moderators on response, remission, and dropout$_{ANY}$.

3.3. Balanced treatment recommendations

Balanced benefits based on the combined covariate action were assessed for individual antidepressants. The balance between efficacy (response) and tolerability (dropout$_{AE}$) is explained in Fig. 2 and illustrated Figs. 3 and 4 (Table 2), while details on other outcomes can be found in the supplementary appendix (Fig. S6).

- Best-balanced antidepressants were suggested to be agomelatine and escitalopram because of their favorable relation between efficacy and tolerability. Pooled effect estimates of agomelatine were found to be mapped on the 1st octant indicating adverse events being overall smaller in effect size than those of efficacy, whereas pooled effect estimates of escitalopram were mapped on the border between the 1st and 8th octant indicating effects of efficacy and tolerability being overall equal in size (Fig. 3). Both antidepressants were suggested for ages 30–65 years, which is a larger age range compared to most of the other drugs (Fig. 4).
- Agomelatine was suggested to allow for dose escalation up to 40 mg/day$_{FE}$, corresponding to approximately 50 mg/day agomelatine, which is the upper end of the licensed dose range 25–50 mg/day (Table 2 and Fig. 4). This dose recommendation has been constrained to 40 mg/day$_{FE}$ because the actual dose range for agomelatine investigated in the trials was limited to 38 mg/day$_{FE}$; any higher doses suggested by the NMA results might be affected by extrapolation [37], most likely due to the direct and indirect evidence coming from comparisons with escitalopram, fluoxetine, or venlafaxine Fig. S3, which were dosed > 40 mg/day$_{FE}$ (Table 2).

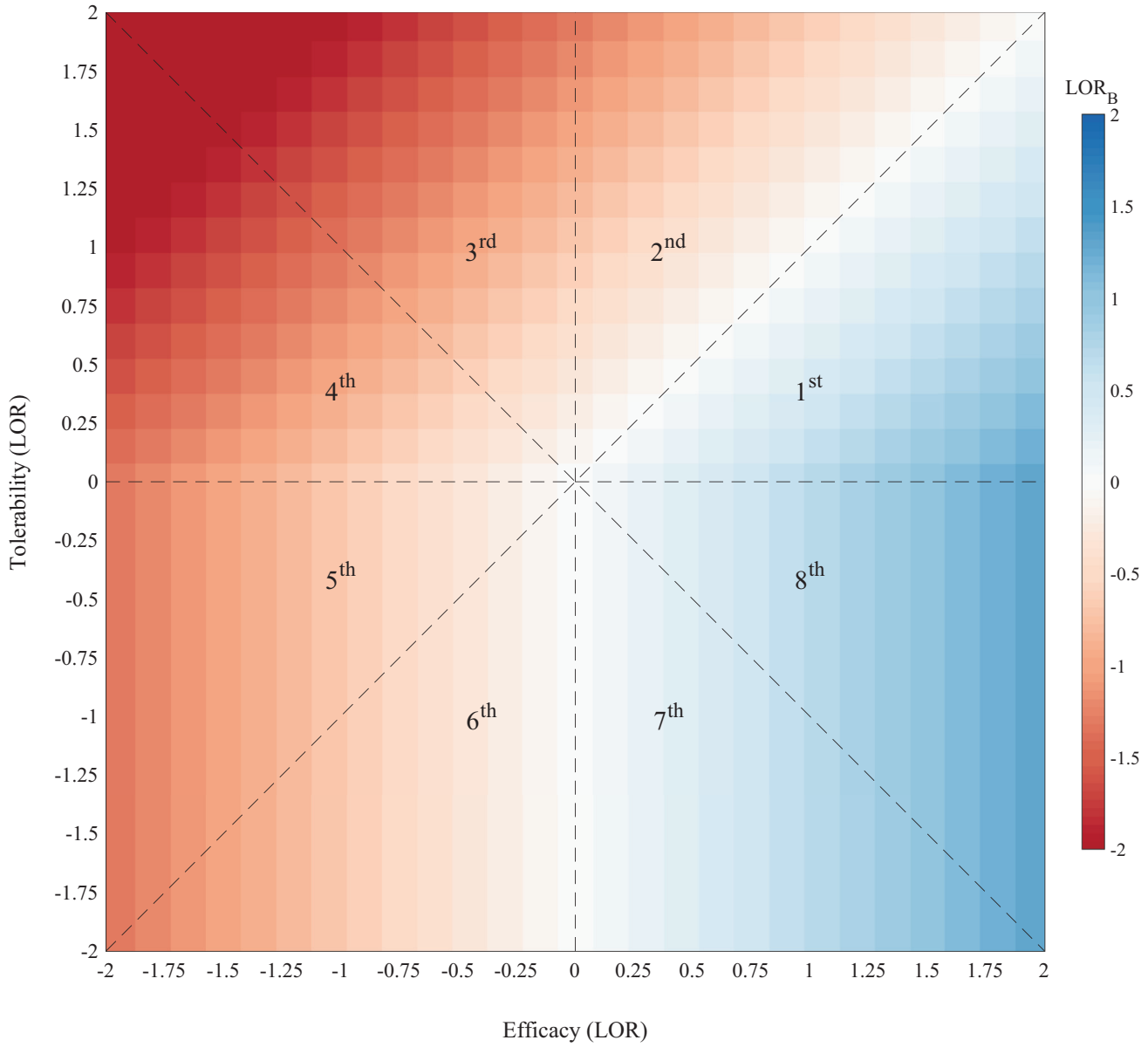

Fig. 2. *Color scheme defining balanced mapping.* Two-dimensional graph illustrating the color scheme used to define the balance mapping between efficacy (response) versus tolerability ($dropout_{AE}$) on the balanced log odds ratio (LOR_B) scale. Blue colors indicate a balance in favor of efficacy, and vice versa, red color indicate a balance in favor of dropouts. Octants quantifying the balance between efficacy and tolerability are numbered.

- Escitalopram was suggested to allow for dose escalation up to 60 mg/day_{FE} (Fig. 4), also constrained to the actual dose range available in the data. This dose is slightly above the corresponding licensed dose range (60 mg/day_{FE} corresponds to approximately 27 mg/day escitalopram, licensed dose range 10–20 mg/day, Table 2), and should therefore only be considered if clinically justified. ny higher doses suggested by the NMA results might be affected by extrapolation,[37] most likely due to direct and indirect evidence coming from comparisons with sertraline or venlafaxine Fig. S3, which were dosed up to 80 mg/day_{FE} (Table 2).
- Balanced benefits for most of the other antidepressants were found to be mapped on the 2nd octant indicating an overall imbalance to the disadvantage of efficacy (Fig. 3). Desvenlafaxine, duloxetine, fluoxetine, milnacipran, and vortioxetine were suggested to be escalated until 20–40 mg/day_{FE}, whereas bupropion, citalopram, mirtazapine, paroxetine, and venlafaxine may not be given in doses $>$ 20 mg/day_{FE} (Fig. 4).
- The remaining antidepressants amitriptyline, clomipramine, fluvoxamine, levomilnacipran, reboxetine, sertraline, and trazodone revealed no relevant balanced benefits because of adverse events exceeding efficacy, as mapped on the 2nd or even 3rd octant indicating an imbalance due to low efficacy and/or low tolerability (Figs. 3 and 4). These antidepressants may therefore not be recommended for treatment.
- All antidepressants may require dose reductions in patients $>$ 65 years, in order to account for the nonlinearity in age effects on tolerability.

Discussion

The present analysis demonstrates that the combined covariate action of dose and age is of clinical relevance for balanced antidepressant treatment recommendations. The present results go beyond that

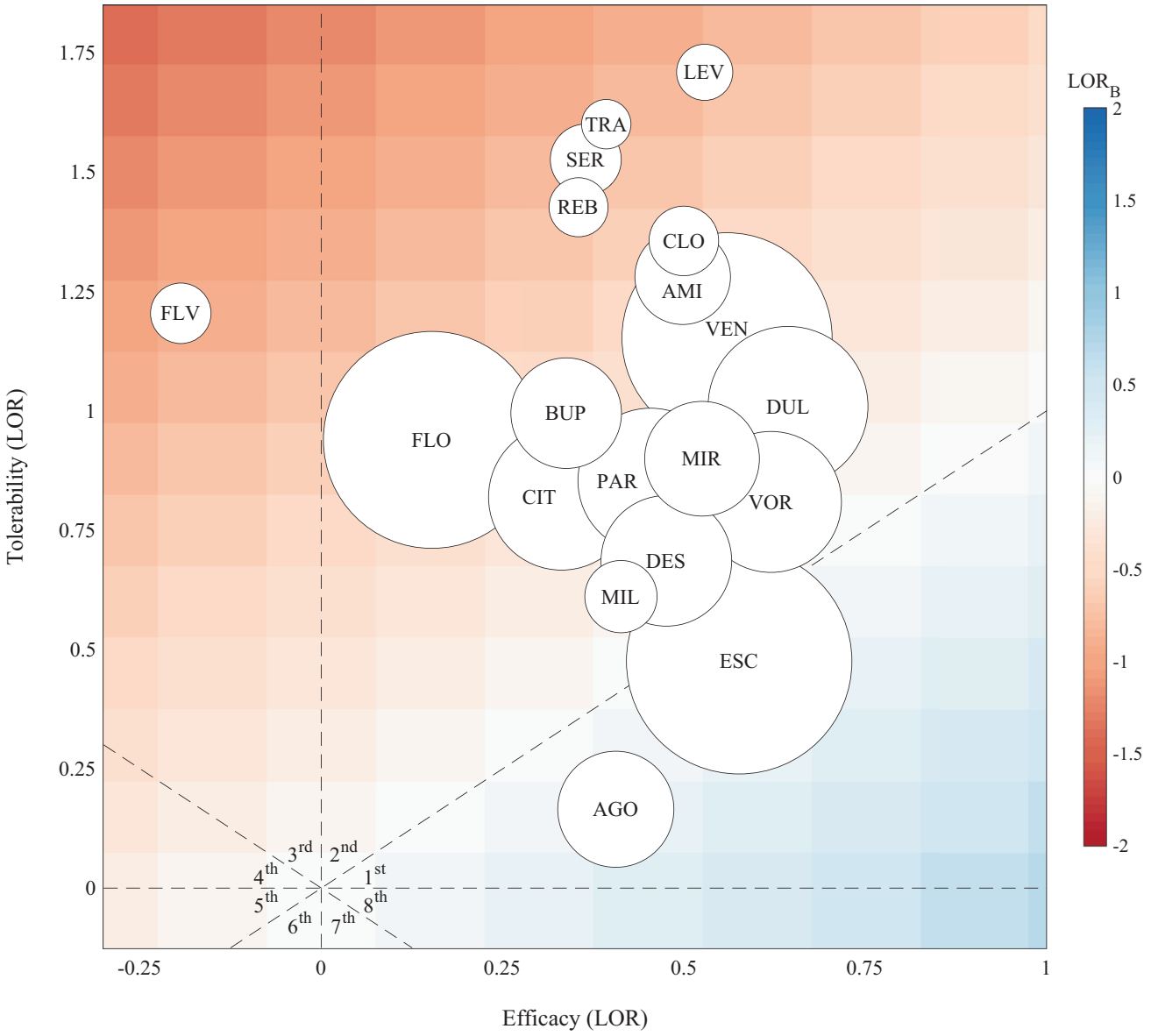

Fig. 3. *Balanced treatment recommendations: average across covariate values.* Two-dimensional graph illustrating the balance between efficacy (response) versus tolerability (dropout$_{AE}$) based on the combined covariate action of dose$_{RCS}$ & age$_{RCS}$ in foxed dose trials. Blue colors indicate a balance in favor of efficacy, and vice versa, red color indicate a balance in favor of dropouts on the balanced log odds ratio (LOR$_B$) scale. Individual drugs are indicated by nodes representing the median across covariate values along the dose and age dimensions. Size of the nodes represent the relative treatment effects weighted by the inverse variance method [55] (i.e., one divided by the standard error squared), such that treatment effects with greater precision (smaller CrIs) are represented by larger points than those with smaller precision (wider CrIs), a method to minimize the imprecision of pooled effect estimates. Octants quantifying the relationship between efficacy and tolerability are numbered. See Fig. S6 for details on all trials.

reported by Furukawa et al. [1] and other earlier dose-response meta-analyses [27–29], in that they demonstrate that dosing recommendations may not be generalized across antidepressants but may be considered drug-specific with age as a potential limiting moderator.

Agomelatine and escitalopram were suggested as favorable balanced antidepressants which may be explained based on their pharmacological profiles. Agomelatine, combining norepinephrine and dopamine disinhibition (NDDI) plus melatonergic agonism [44], has a favorable adverse effect profile mostly due to the fact that it does not affect sexual functioning, weight gain, or metabolic syndrome, and positively regulates sleep quality [45,46]. The balance benefit observed in the present analysis for agomelatine is thus due to its relatively good tolerability and not due to superior efficacy. This is in line with Cipriani et al. [25], who ranked agomelatine as the best acceptable (1st rank) but only moderate efficacious (12th rank) antidepressant (Fig. S7). Its comparable low efficacy may be a reason why agomelatine is still one of the less frequently used antidepressants [47]. The present analysis suggests potential dose escalation until 40 mg/day$_{FE}$, which is the upper limit of its licensed range (Table 2).

Escitalopram, after citalopram one of the most commonly used antidepressants [47], has a unique mechanism among SSRIs. While the exact mechanism is unclear, the most common explanation why escitalopram seems to be more effective than citalopram, is that there is a synaptic interaction for the racemat citalopram (which consists of the S- and R-citalopram enantiomers), in that the presence of R-citalopram somehow inhibits the more active S-citalopram in the binding to the serotonin (5-hydroxytryptamine [5-HT]) site of the serotonin transporter (SERT) [48,49]. Therefore, escitalopram (consisting only of the S-citalopram enantiomer) has a pharmacologically greater therapeutic range and a more rapid mode of action. This raises the possibility of increasing efficacy with increasing dose, which has previously been suggested as useful strategy in MDD [50]. Unlike agomelatine, the favorable balance observed here for escitalopram is therefore equally due to both efficacy (8^{th} rank) and

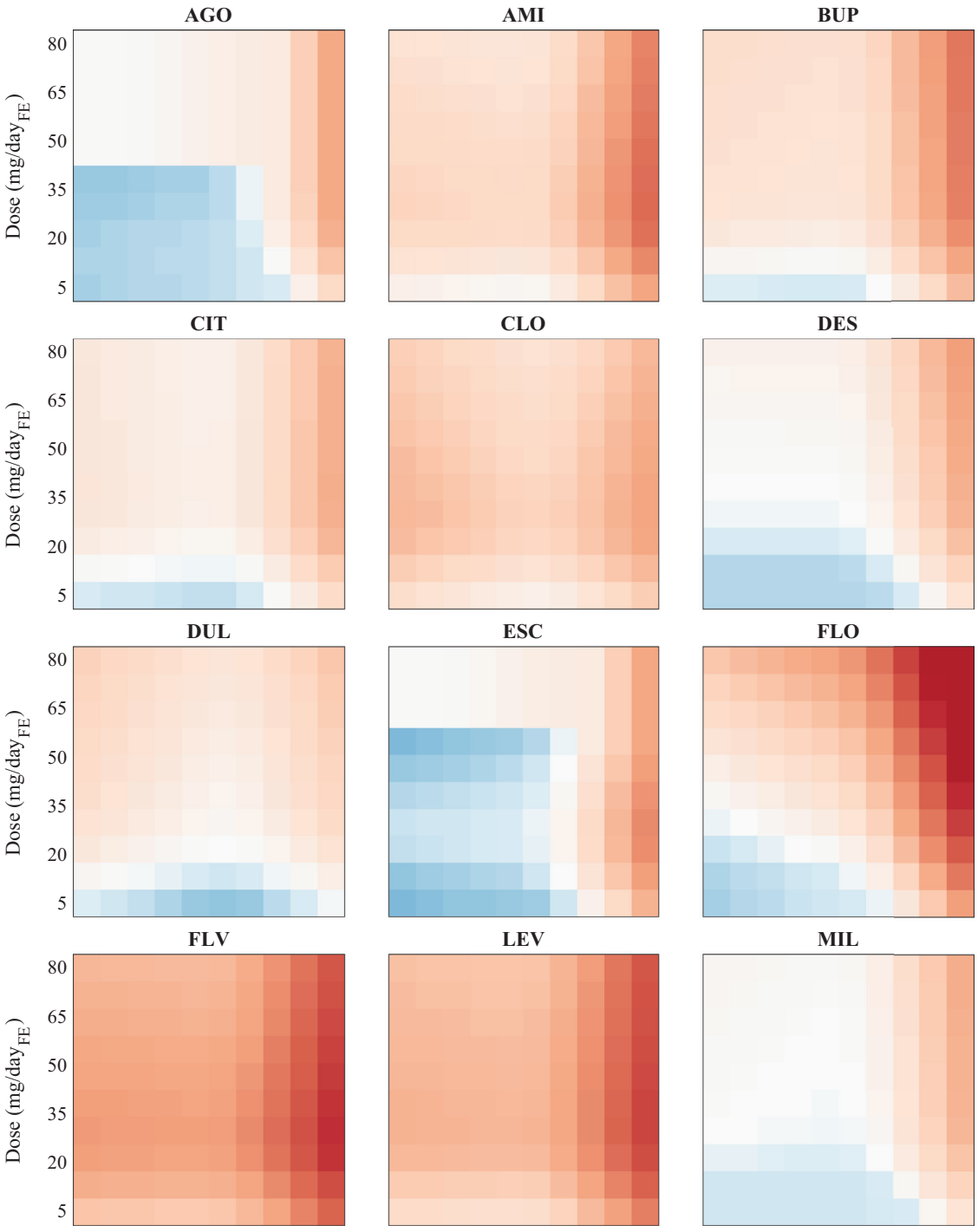

Fig. 4. *Balanced treatment recommendations: as a function of covariate values.* Heatmaps representing balanced benefits between efficacy (response) and tolerability (dropout$_{AE}$) based on the combined covariate action of dose$_{RCS}$ & age$_{RCS}$ in fixed dose trials. Colors code the balance between efficacy and tolerability on the balanced log odds ratio (LOR$_B$) scale, with blue colors indicating a balance in favor of efficacy, and vice versa, red colors indicating the balance in favor of dropouts. The corresponding color scheme mapping the balance on the octants of the two-dimensional coordinate system can be found in Fig. 2. See Fig. S6 for details on all trials.

tolerability (3rd rank), as ranked by Cipriani et al. [25] (Fig. S7). The present analysis suggests potential dose escalation until 60 mg/day$_{FE}$, which is slightly above the upper limit of its licensed range (Table 2).

The remaining antidepressants were found to have balanced benefits within smaller dose ranges. Balanced treatment recommendations suggest that some antidepressants may be given until 20–40 mg/day$_{FE}$ (desvenlafaxine, duloxetine, fluoxetine, milnacipran, and vortioxetine), whereas others may not be used > 20 mg/day$_{FE}$ (bupropion, citalopram, mirtazapine, paroxetine, and venlafaxine). A considerable number of antidepressants (amitriptyline, clomipramine, fluvoxamine, levomilnacipran, reboxetine, sertraline, and trazodone) revealed no balanced benefits at all and may therefore not be recommended for antidepressant treatment because of their questionable clinical benefit.

Limiting the present analysis is the fact that information available on the low dose range (5–40 mg/day$_{FE}$, 82%) was substantially larger than on the high dose range (40–80 mg/day$_{FE}$, 18%) (Fig. S2). Interpretation should therefore consider that effects presented for high dosages may be less reliable due to intra- and extrapolation of covariate information taking place (Fig. S3) [37]. Interpretation should also consider that other conversion methods [27,28,51] than those used

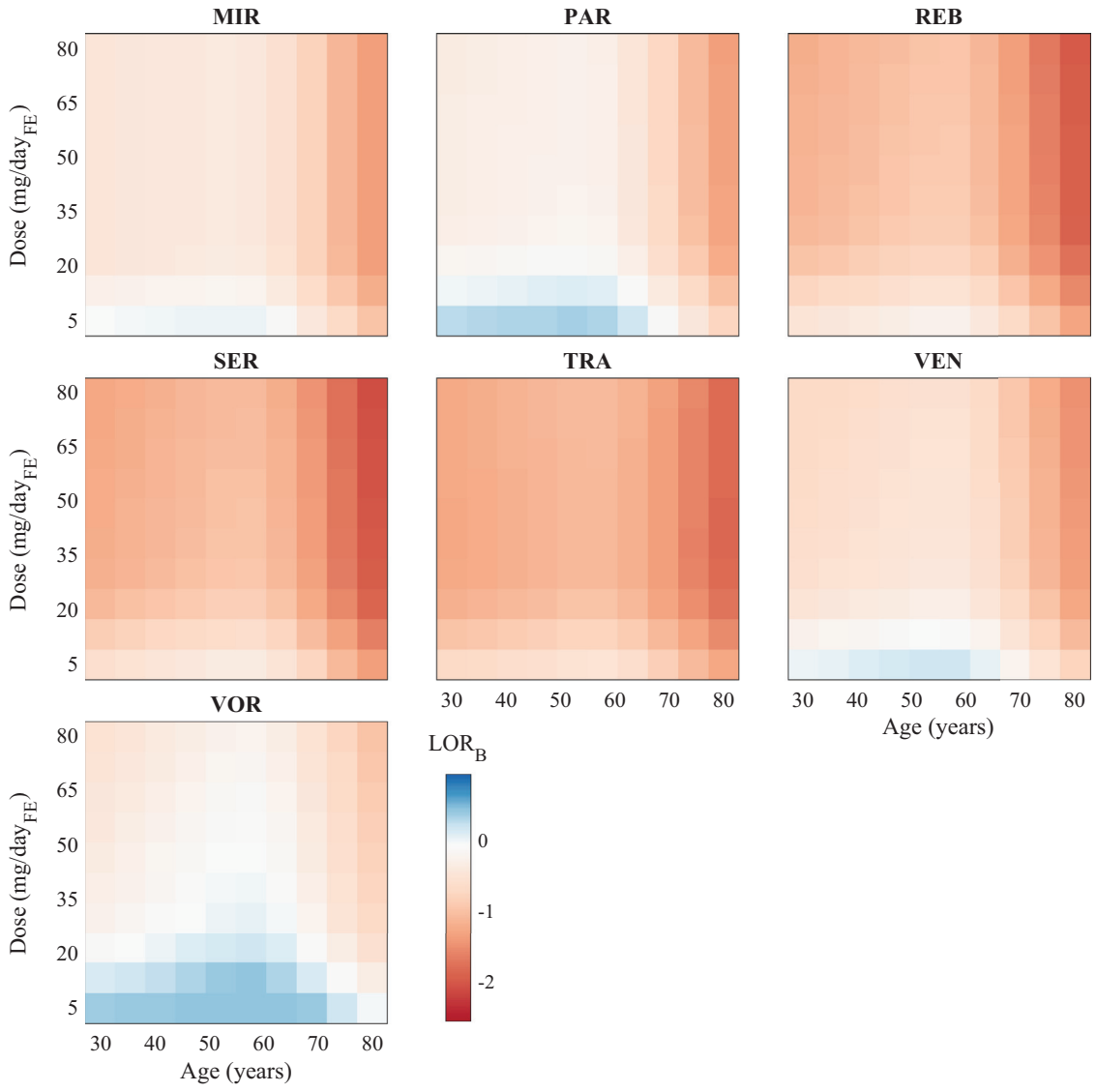

Fig. 4 Continued.

in the present analysis to derive dosage equivalents [2,3] may produce different effects.

Age was suggested as potential limiting moderator for antidepressant dosing recommendations. While doses reported here may be tolerable in patients between 30–65 years of age, patients > 65 years may require dose reductions. Indeed, none of the antidepressants was observed to provide balanced benefits in patients > 70 years because of adverse events exceeding efficacy. Again, limiting the present results is the fact that information available on ages > 65 years (79%) was greater than that on > 65 years (21%), as well as that no trials included patients > 30 years (Fig. S2), which ultimately limits the clinical interferences to be made on both ends of the age spectrum. The nonlinearity of the observed age effects however supports earlier reports that the risk-benefit ratio is most favorable for adults between 25 and 65 years, while both younger adults > 25 years, due to an increased risk of suicidality [23] and hyperarousal events [24], as well as elderly patients > 65 years, due to more side effects [11–16], pharmacodynamic tolerance [19], and suicidality [20–22], may not respond as well to antidepressants. Considering the presented balanced dosing recommendations may thus not necessarily lead to better response rates, but may keep tolerability at endurable levels, which is important for treatment compliance and adherence.

It should be emphasized that the presented balanced treatment recommendations are based on statistical significance and not clinical significance. Criteria for clinical significance in antidepressant treatment have earlier been suggested by the National Institute for Health and Clinical Excellence (NICE) (Cohen's d > 0.5) [52], but have later been criticized for being arbitrary and should therefore be interpreted with caution [53]. A measure of clinical significance for antidepressant treatment however would be helpful to judge wether the presented balanced recommendations are transferable to antidepressants' real-world benefits.

It should also be considered that other covariates, such as depression severity or gender, as well as plausible risk of bias not accounted for by the covariates may also affect treatment recommendations, with the latter being primarily due to study limitations, imprecision, and publication bias, as revealed by an earlier sensitivity analysis on the same dataset [54].

In conclusion, the present analysis based on Bayesian NMA may be viewed as a next step towards optimizing dosage recommendations for antidepressant treatment in dependence on age. The results may inform researchers and guideline developers to reconsider the nonlinearity of dose-age dependencies before generalizing antidepressant treatment recommendations in adult MDD.

Table 2
Balanced dose recommendations. Listed are the balanced dose recommendations (rounded) derived from the primary analysis based on fixed dose trials. Doses were converted to 20 mg/day fluoxetine equivalents (mg/day$_{FE}$) using the conversion suggested by Hayasaka et al., [2] supplemented by the daily defined dose (DDD) method. [3] Licensed dosage ranges are listed as approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Accepted ranges are listed as recommended in main clinical guidelines. [25] See **Tab. S4** for details on all trials.

	Dose recommendation mg/day$_{FE}$	Dose mean (range) equivalent mg/day$_{FE}$	Licensed range equivalent mg/day$_{FE}$	Licensed range mg/day	Accepted range mg/day
AGO	40	24 (19–38)	19–38	25–50	-
AMI	-	46 (25–65)	25–65	75–200	50–300
BUP	10	36 (23–52)	34–52	300–450	200–450
CIT	15	31 (20–60)	20–40	20–40	20–60
CLO	-	34 (21–52)	10–86	30–250	10–300
DES	40	28 (20–40)	20–40	50–100	-
DUL	25	21 (13–40)	13–40	40–120	30–120
ESC	60	33 (22–62)	22–44	10–20	10–30
FLO	30	25 (20–60)	20–80	20–80	10–80
FLV	-	49 (14–84)	14–84	50–300	-
LEV	-	14 (8–24)	8–24	40–120	20–120
MIL	40	27 (10–40)	10–40	50–200	-
MIR	30	25 (12–35)	12–35	15–45	-
PAR	15	30 (24–47)	24–59	20–50	20-6
REB	-	26 (14–35)	28–42	8–12	4–12
SER	-	45 (20–81)	20–81	50–200	-
TRA	-	12 (5–15)	15–40	150–400	150–600
VEN	10	41 (20–100)	20–100	75–375	-
VOR	40	22 (10–40)	10–40	5–20	-

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Ethics committee approval

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Data sharing

Results obtained from the analysis are shared in the supplementary appendix.

Declaration of Competing Interest

The author declares no competing interests.

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Supplementary material

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2019.11.012

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