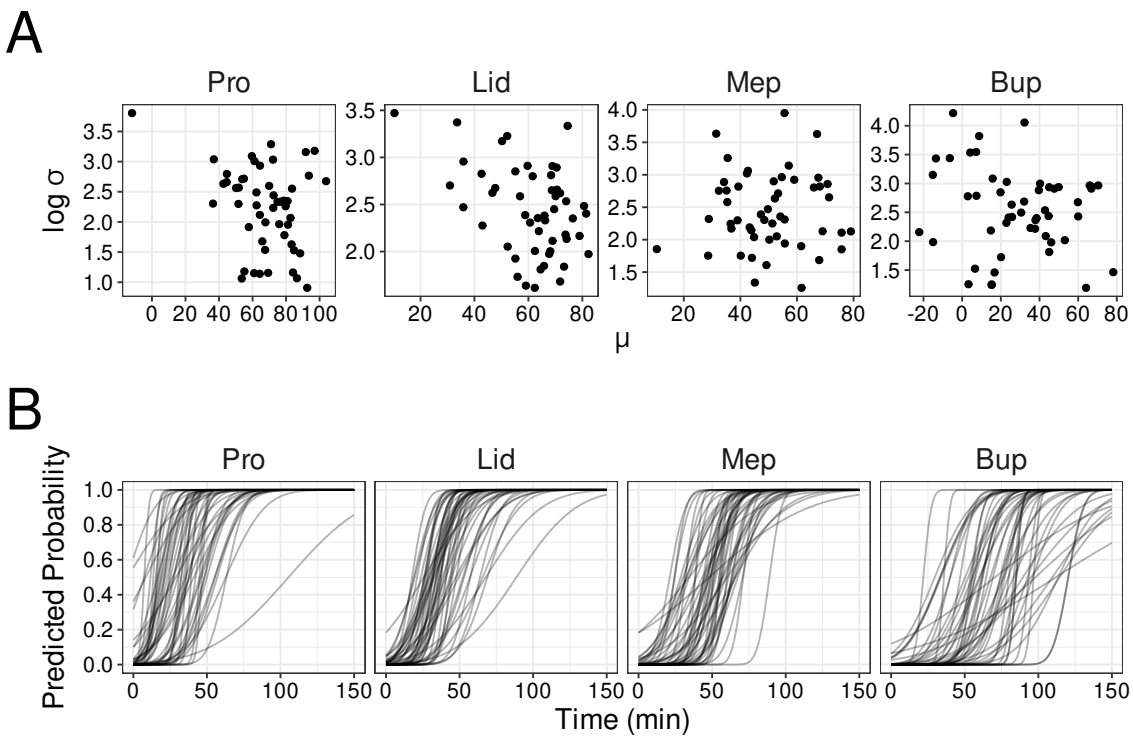

Figure 1: Correlation of parameters between μ and $\log \sigma$ in animal experiments. (A) scatter plot of μ and $\log \sigma$ in each drug, and (B) Predicted probability curve in each drug and individual.

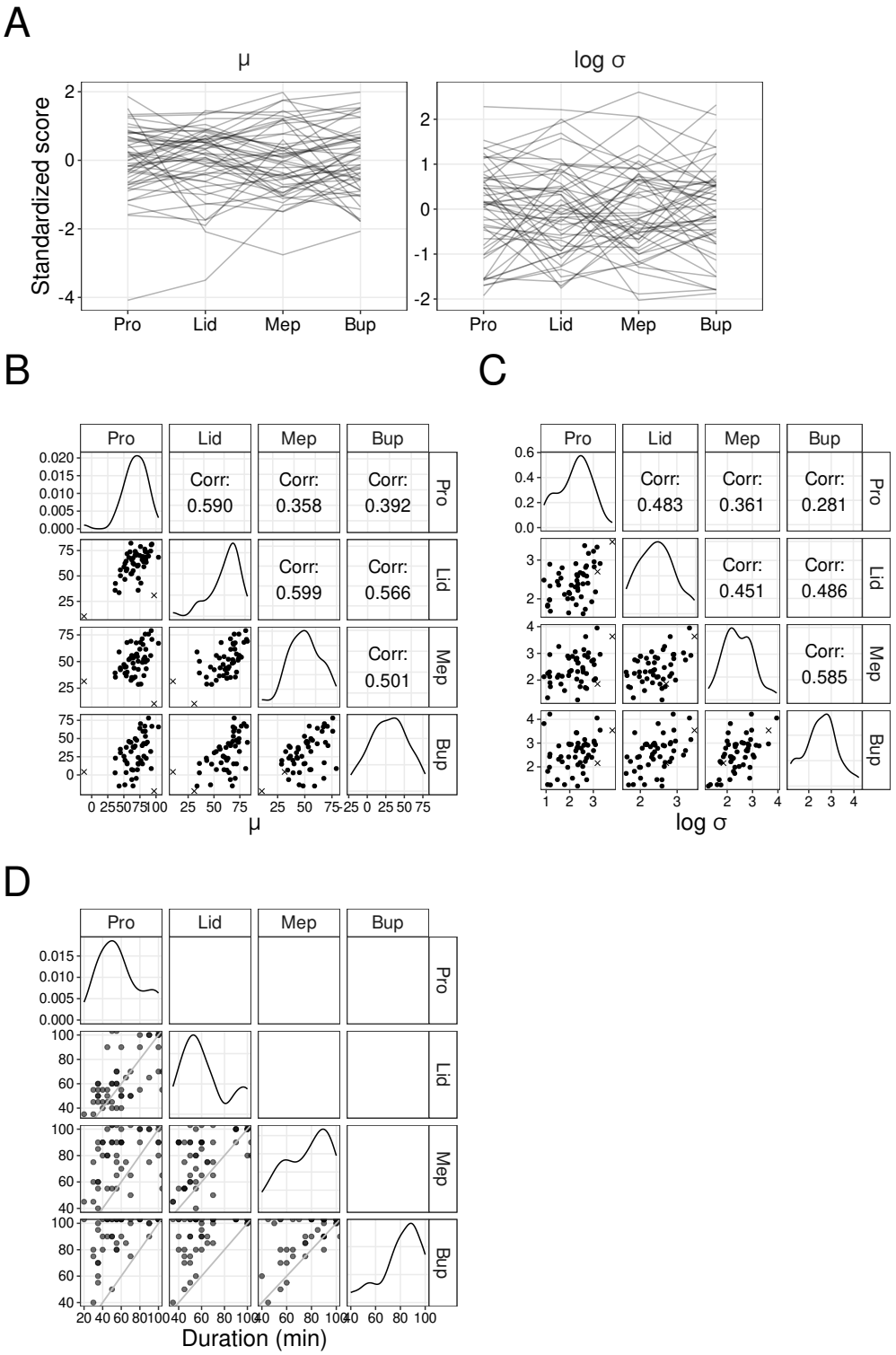

Figure 2: Correlation of parameters among drugs in animal experiments.

Table 1: Correlation coefficients between μ and $\log \sigma$ ($r_{\mu-\log \sigma}$)

Drug	all data ($n = 51$)	without outliers ($n = 49$)
Pro	−0.308	−0.219
Lid	−0.415	−0.301
Mep	0.012	0.014
Bup	−0.154	−0.160

Table 2: Correlation coefficients among drugs

	all data ($n = 51$)		without outliers ($n = 49$)	
Combination	r_μ	$r_{\log \sigma}$	r_μ	$r_{\log \sigma}$
Pro–Lid	0.590	0.483	0.568	0.416
Pro–Mep	0.358	0.361	0.467	0.336
Pro–Bup	0.392	0.281	0.498	0.257
Lid–Mep	0.599	0.451	0.526	0.414
Lid–Bup	0.566	0.486	0.527	0.466
Mep–Bup	0.501	0.585	0.420	0.559

Table 3: Parameters used in following simulations

Drug	μ_0	s_{μ_0}	$\log \sigma_0$	$s_{\log \sigma_0}$	$r_{\mu-\log \sigma}$	Combination	r_μ	$r_{\log \sigma}$
Pro	68	10	2.2	0.4	-0.22	Pro–Lid	0.57	0.42
Lid	61	7	2.4	0.4	-0.30	Pro–Mep	0.47	0.34
Mep	50	7	2.4	0.4	-0.01	Pro–Bup	0.50	0.26
Bup	30	13	2.5	0.5	-0.16	Lid–Mep	0.53	0.41
						Lid–Bup	0.53	0.47
						Mep–Bup	0.42	0.56

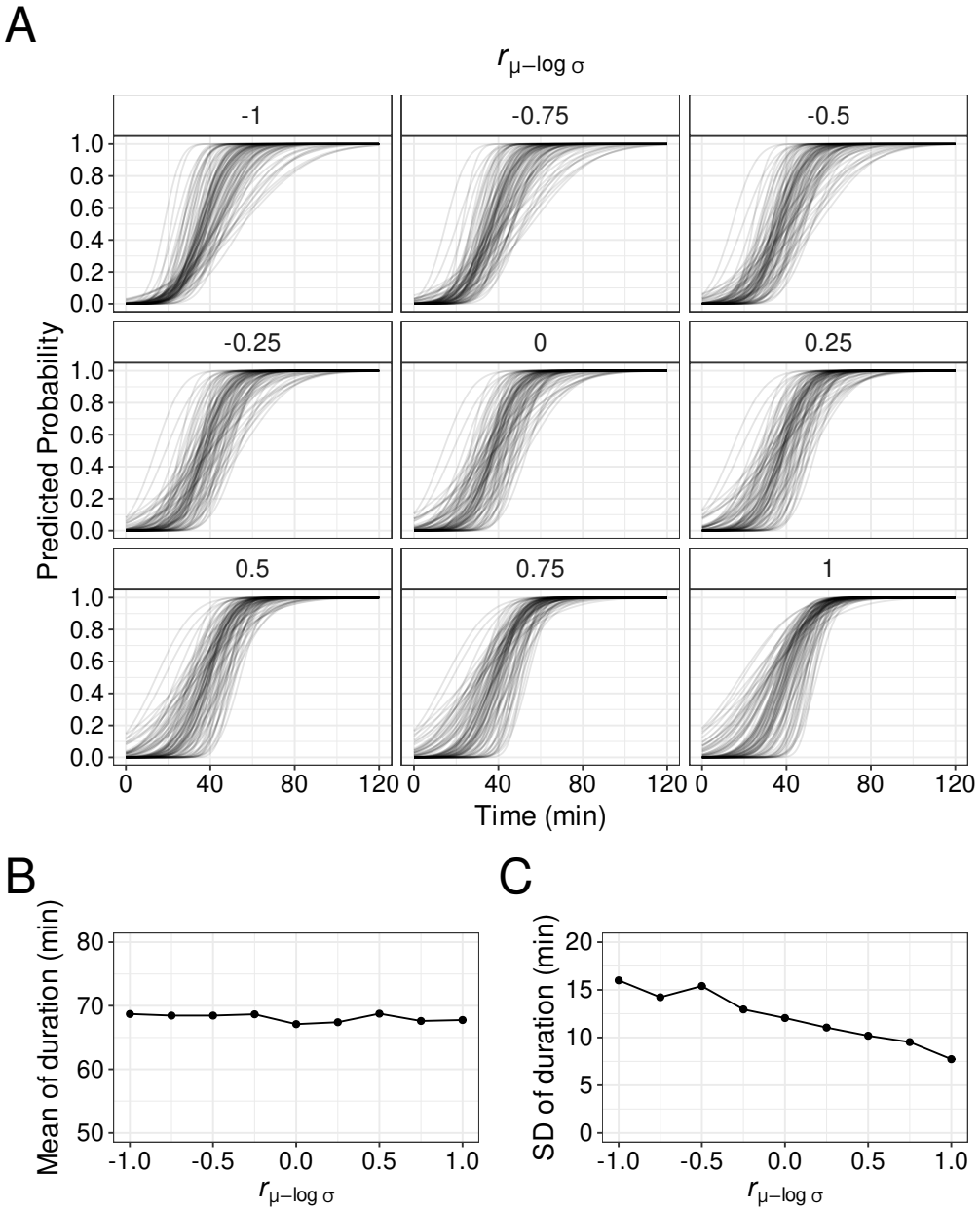

Figure 3: Effect of correlation of parameters between μ and $\log\sigma$ ($r_{\mu-\log\sigma}$) on duration of Lid in simulation.

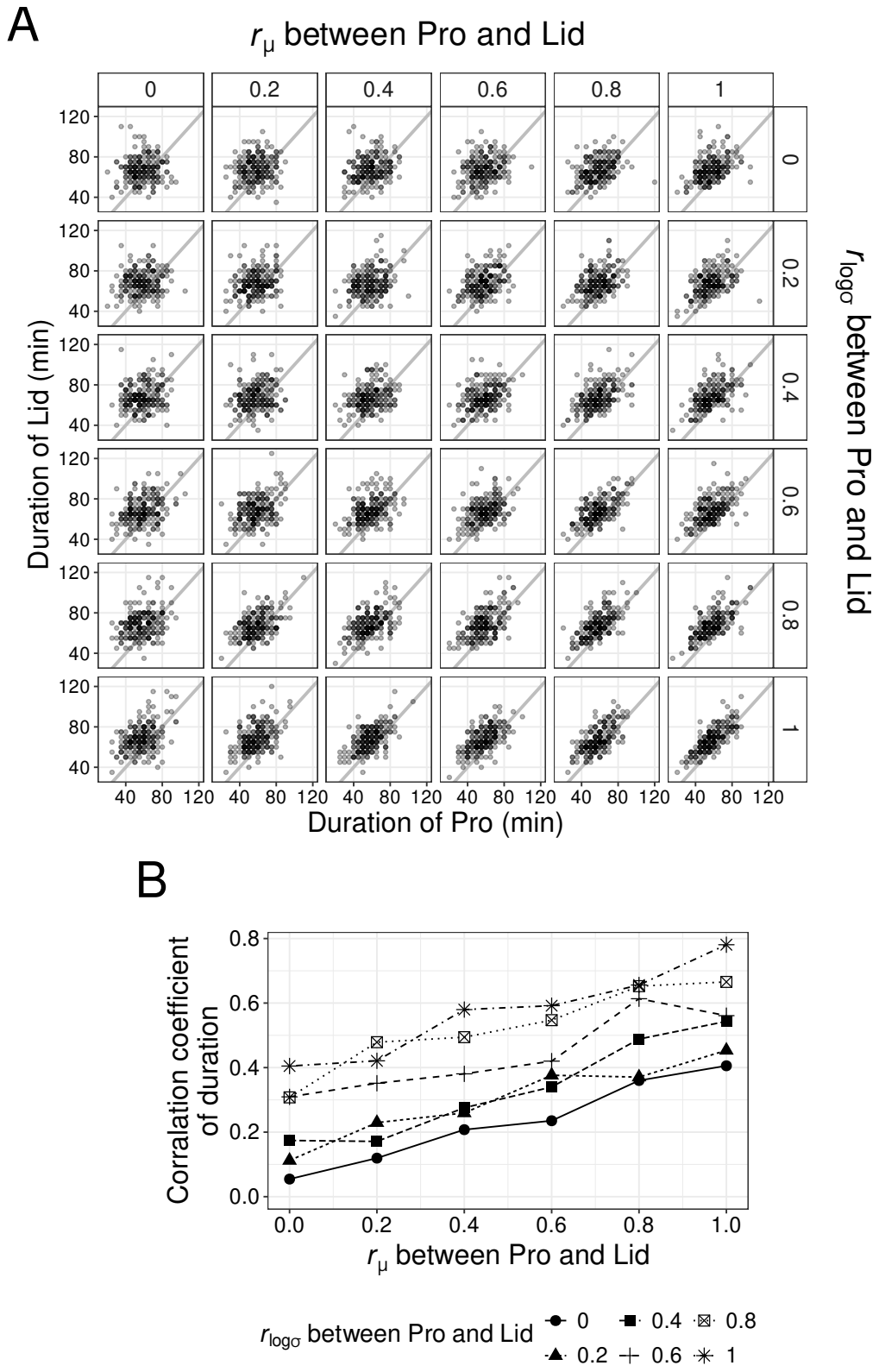

Figure 4: Effect of correlation of parameters (r_μ and $r_{\log\sigma}$) between Pro and Lid on duration in simulation ($r_{\mu-\log\sigma}$ is set to 0). (A) Relation of durations between Pro and Lid. (B) Correlation coefficients of duration in several parameters.

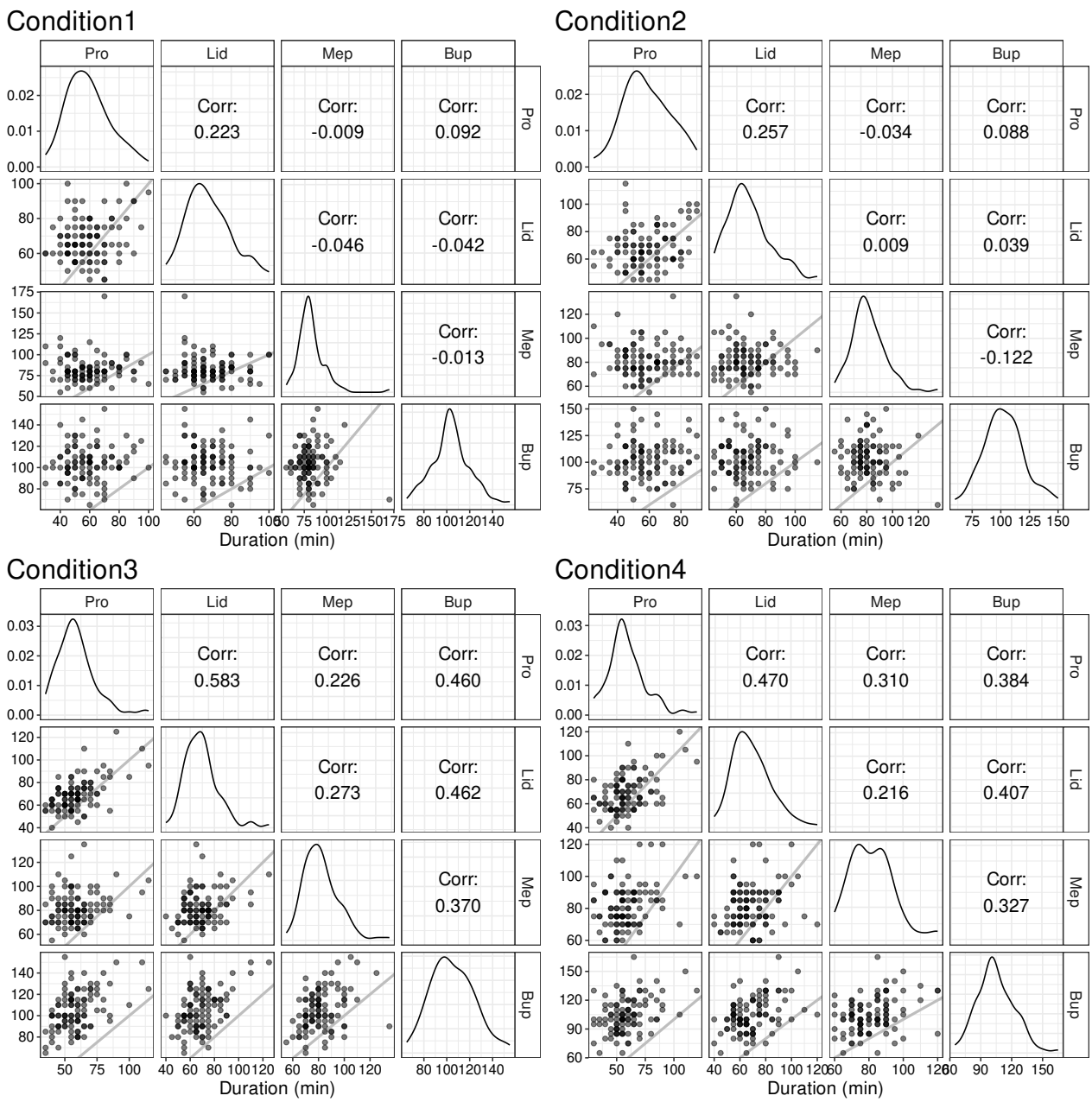

Figure 5: Effect of correlation of parameters among drugs on duration in simulation.

Table 4: Effect of correlation coefficients on duration among drugs

	Condition 1	Condition 2	Condition 3	Condition 4
$r_{\mu-\log\sigma}$	0	*	0	*
r_{μ} and $r_{\log\sigma}$	0	0	*	*
Pro–Lid	0.223	0.257	0.583	0.470
Pro–Mep	−0.009	−0.034	0.226	0.310
Pro–Bup	0.092	0.088	0.460	0.384
Lid–Mep	−0.046	0.009	0.273	0.216
Lid–Bup	−0.042	0.039	0.462	0.407
Mep–Bup	−0.013	−0.122	0.370	0.327

*Parameters in Table 3 were used.

Table 5: Median of duration of local anesthetic agents under each condition

Drug	Condition	n	Events	Median [95% CI]
Pro	Raw data	51	48	55.0 [50.0, 65.0]
	Condition 1	100	100	57.5 [55.0, 60.0]
	Condition 2	100	100	55.0 [55.0, 60.0]
	Condition 3	100	100	55.0 [55.0, 60.0]
	Condition 4	100	100	55.0 [55.0, 60.0]
Lid	Raw data	51	47	60.0 [55.0, 70.0]
	Condition 1	100	100	65.0 [65.0, 70.0]
	Condition 2	100	100	65.0 [65.0, 70.0]
	Condition 3	100	100	70.0 [65.0, 70.0]
	Condition 4	100	100	65.0 [65.0, 70.0]
Mep	Raw data	51	45	85.0 [75.0, 90.0]
	Condition 1	100	100	80.0 [80.0, 80.0]
	Condition 2	100	100	80.0 [75.0, 85.0]
	Condition 3	100	100	80.0 [80.0, 85.0]
	Condition 4	100	100	80.0 [75.0, 85.0]
Bup	Raw data	51	25	– [90.0, –]
	Condition 1	100	100	105.0 [100.0, 105.0]
	Condition 2	100	100	100.0 [100.0, 105.0]
	Condition 3	100	100	100.0 [100.0, 110.0]
	Condition 4	100	100	102.5 [100.0, 105.0]
Lid+Adr	Raw data	51	8	– [–, –]
	Condition 1	100	35	– [–, –]
	Condition 2	100	38	– [–, –]
	Condition 3	100	38	– [–, –]
	Condition 4	100	42	– [180.0, –]

Table 6: Comparison of duration between Pro and Lid

	Comparison	Raw data	Condition 1	Condition 2	Condition 3	Condition 4
Parameter	Pro > Lid	31 (60.8%)	69 (69.0%)	73 (73.0%)	79 (79.0%)	80 (80.0%)
	Pro < Lid	20 (39.2%)	31 (31.0%)	27 (27.0%)	21 (21.0%)	20 (20.0%)
Duration	Pro < Lid	29 (56.9%)	68 (68.0%)	67 (67.0%)	75 (75.0%)	70 (70.0%)
	Pro = Lid	6 (11.8%)	5 (5.0%)	4 (4.0%)	9 (9.0%)	11 (11.0%)
	Pro > Lid	15 (29.4%)	27 (27.0%)	29 (29.0%)	16 (16.0%)	19 (19.0%)
	both censored	1 (2.0%)	—	—	—	—

Supplementary Table 1: Spearman's rank correlation coefficients of duration among drugs

Combination	all data (n = 51)	without outliers (n = 49)
Pro–Lid	0.592	0.603
Pro–Mep	0.388	0.382
Pro–Bup	0.505	0.509
Lid–Mep	0.508	0.457
Lid–Bup	0.434	0.406
Mep–Bup	0.518	0.498

Supplementary Table 2: Analysis by Linear Mixed-Effects Models with interaction

effect	group	term	estimate	std.error	statistic	df	p.value
fixed		(Intercept)	0.083	0.014	5.841	12.4	0.000
fixed		r_mean	0.398	0.012	31.931	277.0	0.000
fixed		r_logSigma	0.267	0.012	21.445	277.0	0.000
fixed		r_mean:r_logSigma	0.020	0.021	0.973	277.0	0.331
ran_pars	seed_param	sd__(Intercept)	0.034				
ran_pars	Residual	sd__Observation	0.041				

Supplementary Table 3: Effect of Spearman's rank correlation coefficients on duration among drugs

	Condition 1	Condition 2	Condition 3	Condition 4
$r_{\mu-\log\sigma}$	0	*	0	*
r_μ and $r_{\log\sigma}$	0	0	*	*
Pro–Lid	0.137	0.200	0.488	0.372
Pro–Mep	0.014	−0.027	0.177	0.262
Pro–Bup	0.083	0.084	0.405	0.356
Lid–Mep	0.013	0.032	0.201	0.201
Lid–Bup	−0.057	0.040	0.367	0.369
Mep–Bup	0.060	−0.061	0.343	0.297

*Parameters in Table 3 were used.