

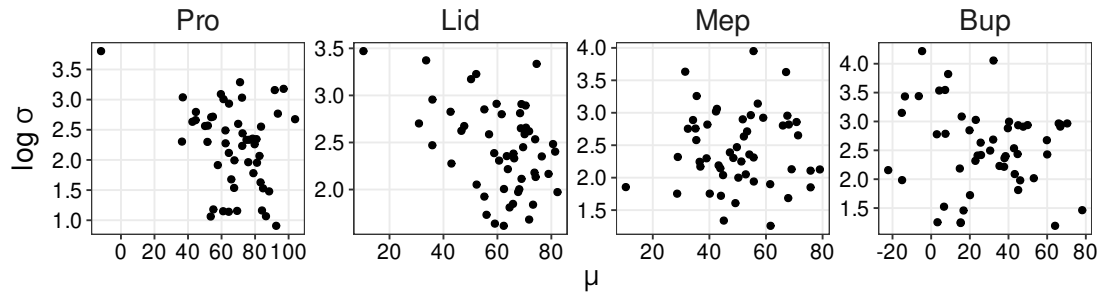
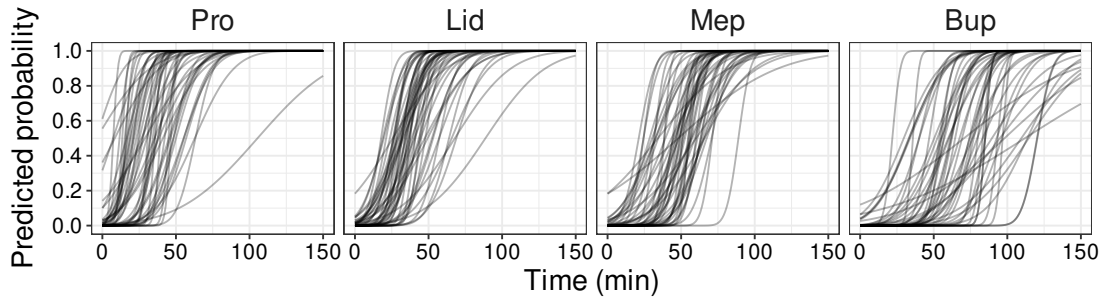
**A****B**

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

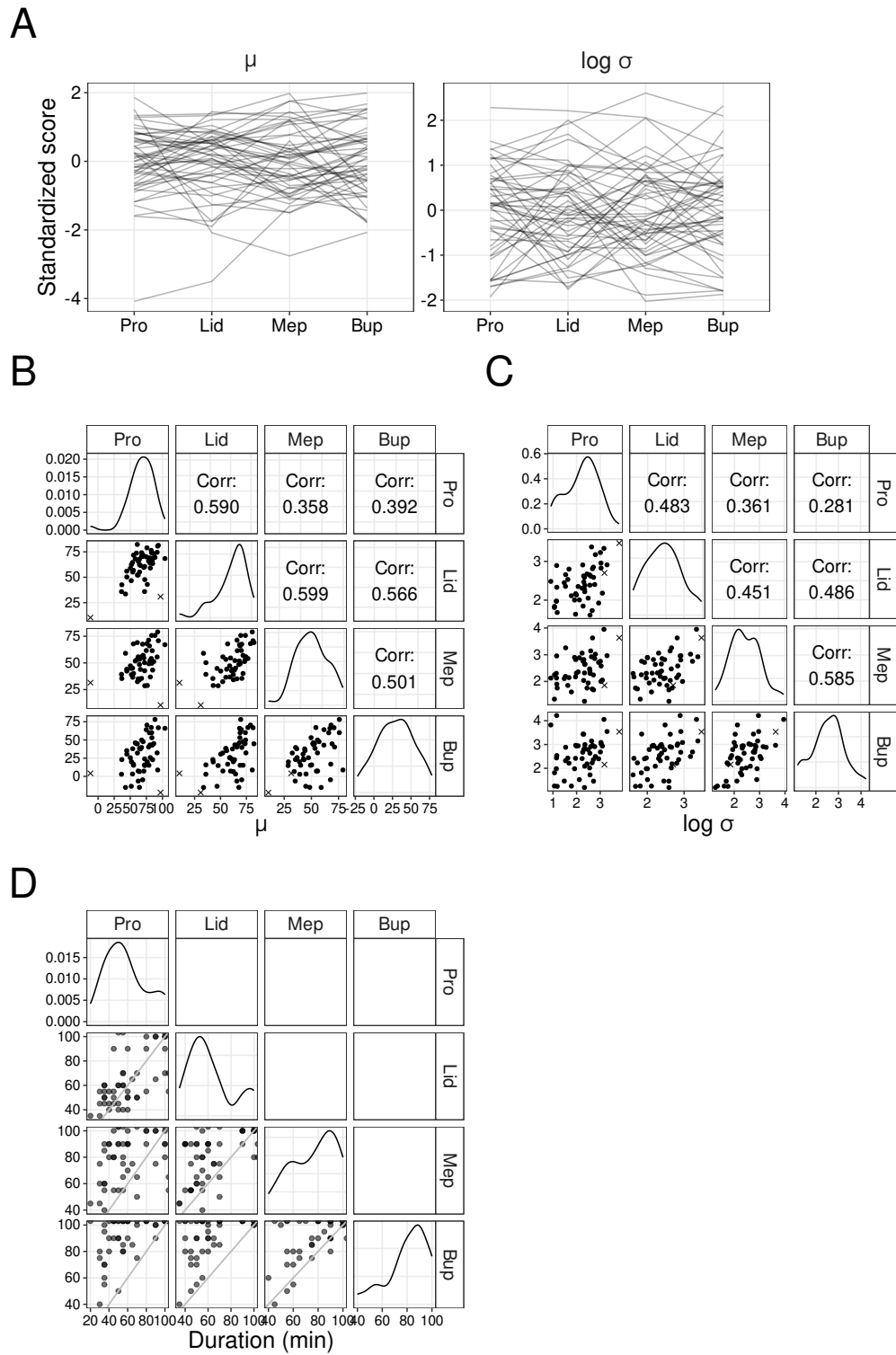


Figure 2: Correlation of parameters among drugs in animal experiments.

Table 1: Correlation coefficients between  $\mu$  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

Combination	all data ( $n = 51$ )		without outliers ( $n = 49$ )	
	$r_{\mu}$	$r_{\log \sigma}$	$r_{\mu}$	$r_{\log \sigma}$
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 simulations

Drug	$\mu_0$	$s_{\mu_0}$	$\log \sigma_0$	$s_{\log \sigma_0}$	$r_{\mu-\log \sigma}$	Combination	$r_{\mu}$	$r_{\log \sigma}$
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

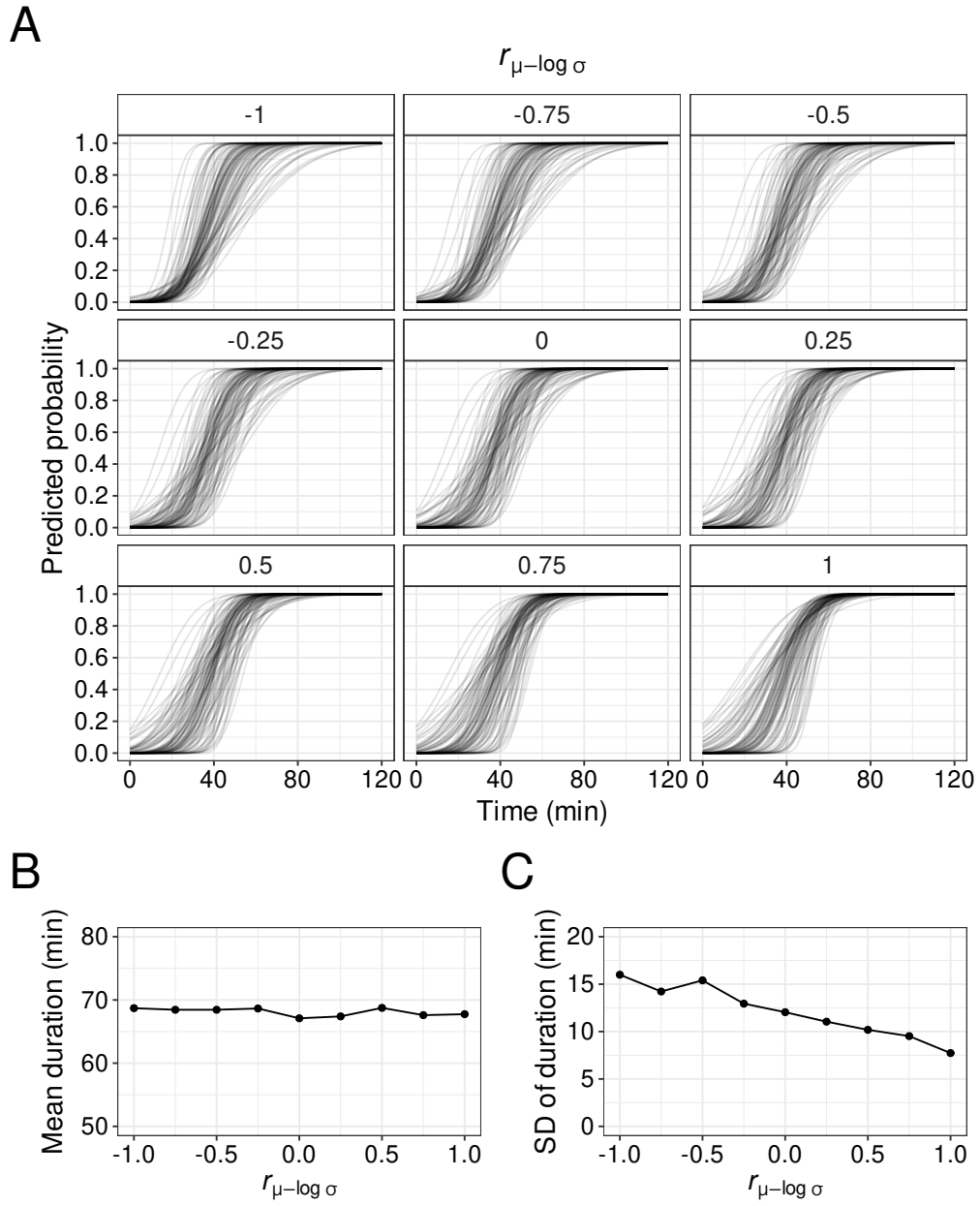


Figure 3: Effect of correlation of parameters between  $\mu$  and  $\log \sigma$  ( $r_{\mu-\log \sigma}$ ) on duration of Lid in simulation.

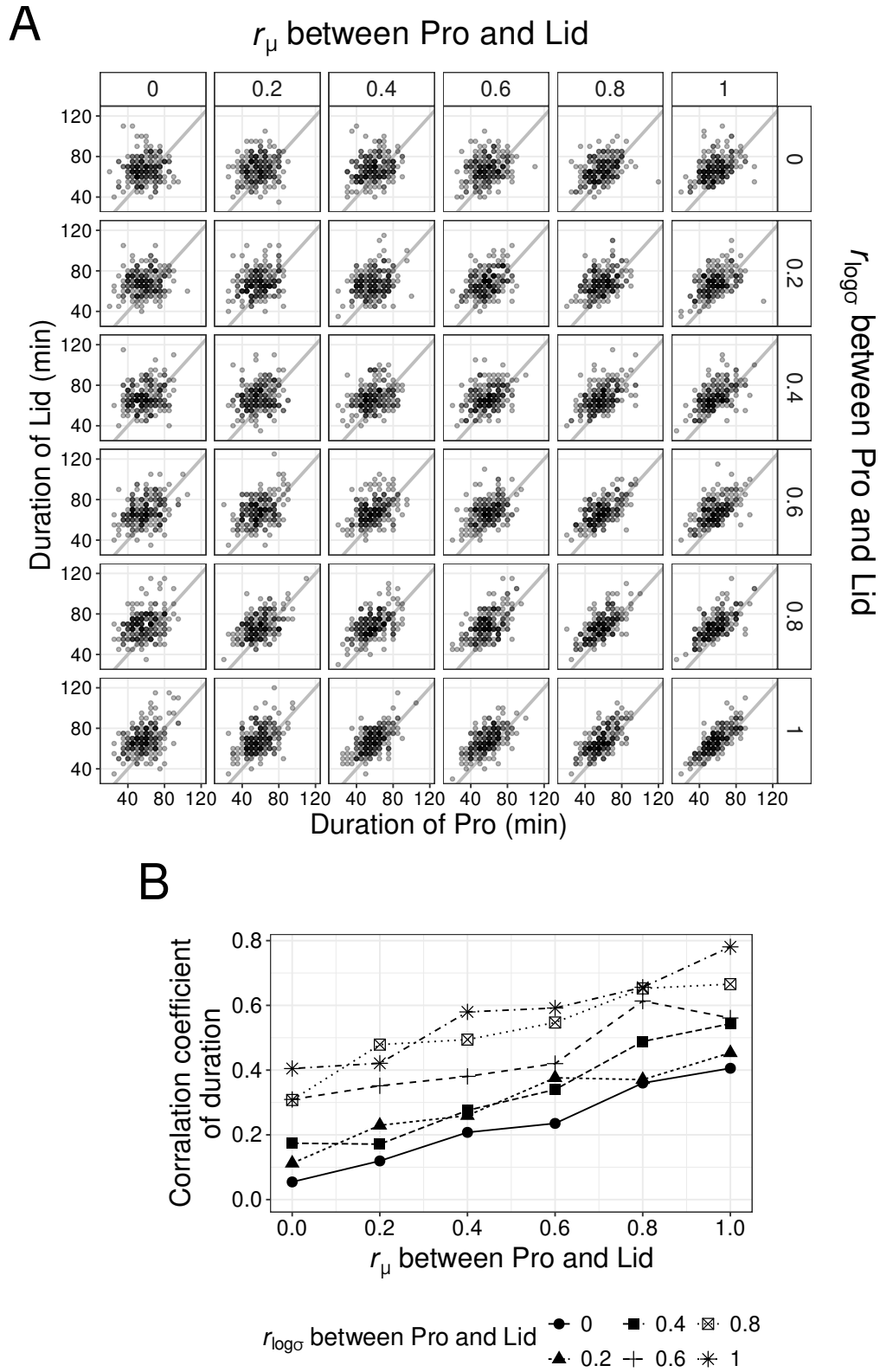
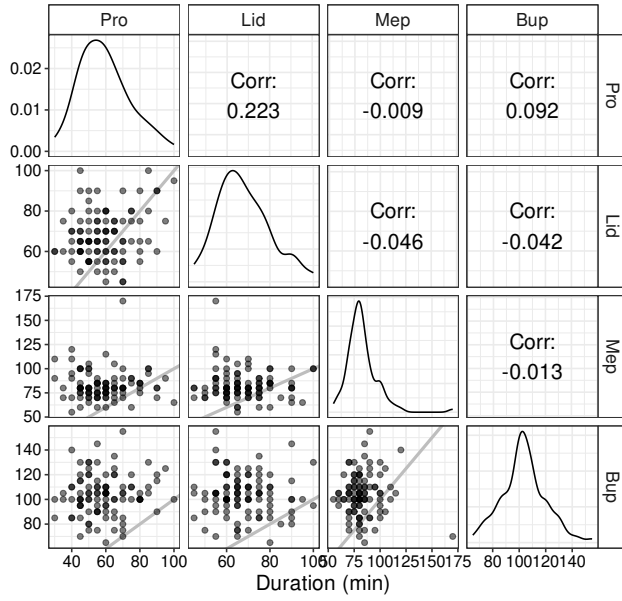
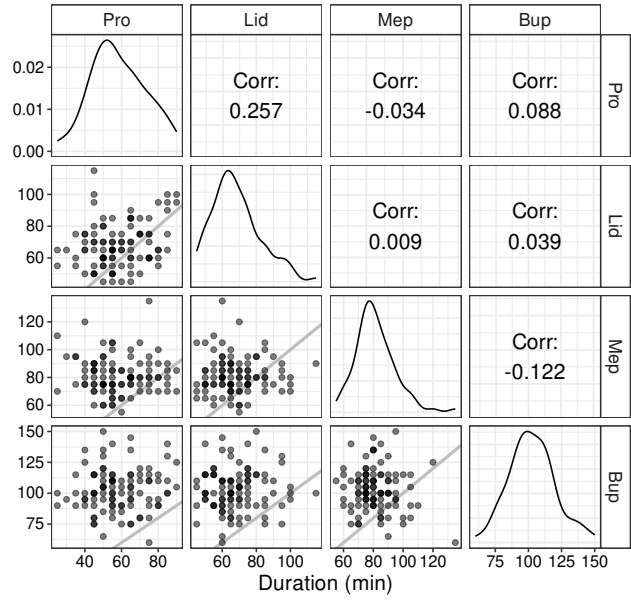


Figure 4: Effect of correlation of parameters ( $r_\mu$  and  $r_{\log \sigma}$ ) between Pro and Lid on duration in simulation ( $r_{\mu-\log \sigma}$  is set to 0). (A) Relation of durations between Pro and Lid. (B) Correlation coefficients of duration in several parameters.

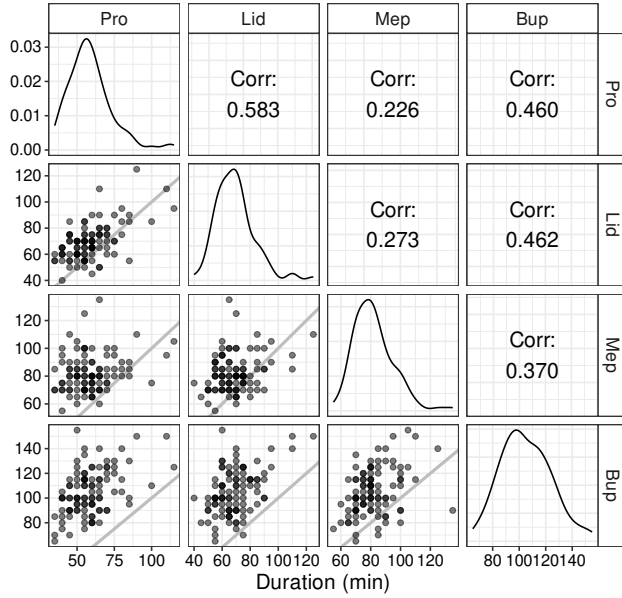
Condition1



Condition2



Condition3



Condition4

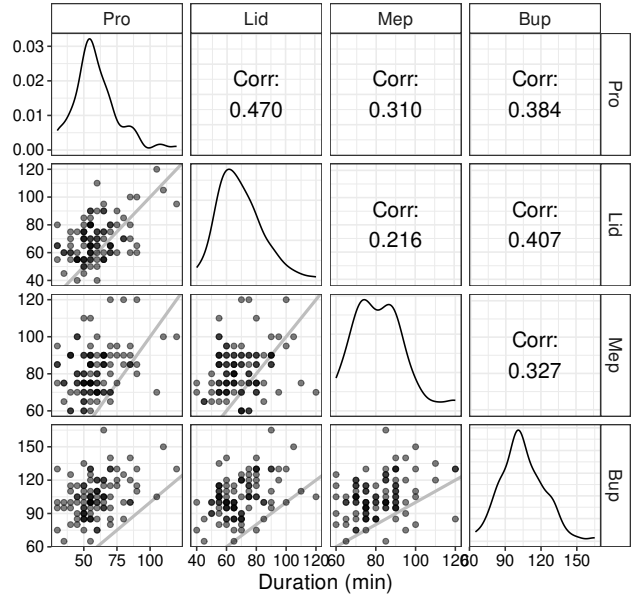


Figure 5: Effect of correlation of parameters among drugs on duration in simulation.

Table 4: Effect of correlation coefficients on duration among drugs

	Condition 1	Condition 2	Condition 3	Condition 4
$r_{\mu-\log \sigma}$	0	*	0	*
$r_{\mu}$ 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	*
$r_{\mu}$ 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.