Supporting information

Antidepressants can induce mutation and enhance persistence towards multiple antibiotics

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Supplementary Figures

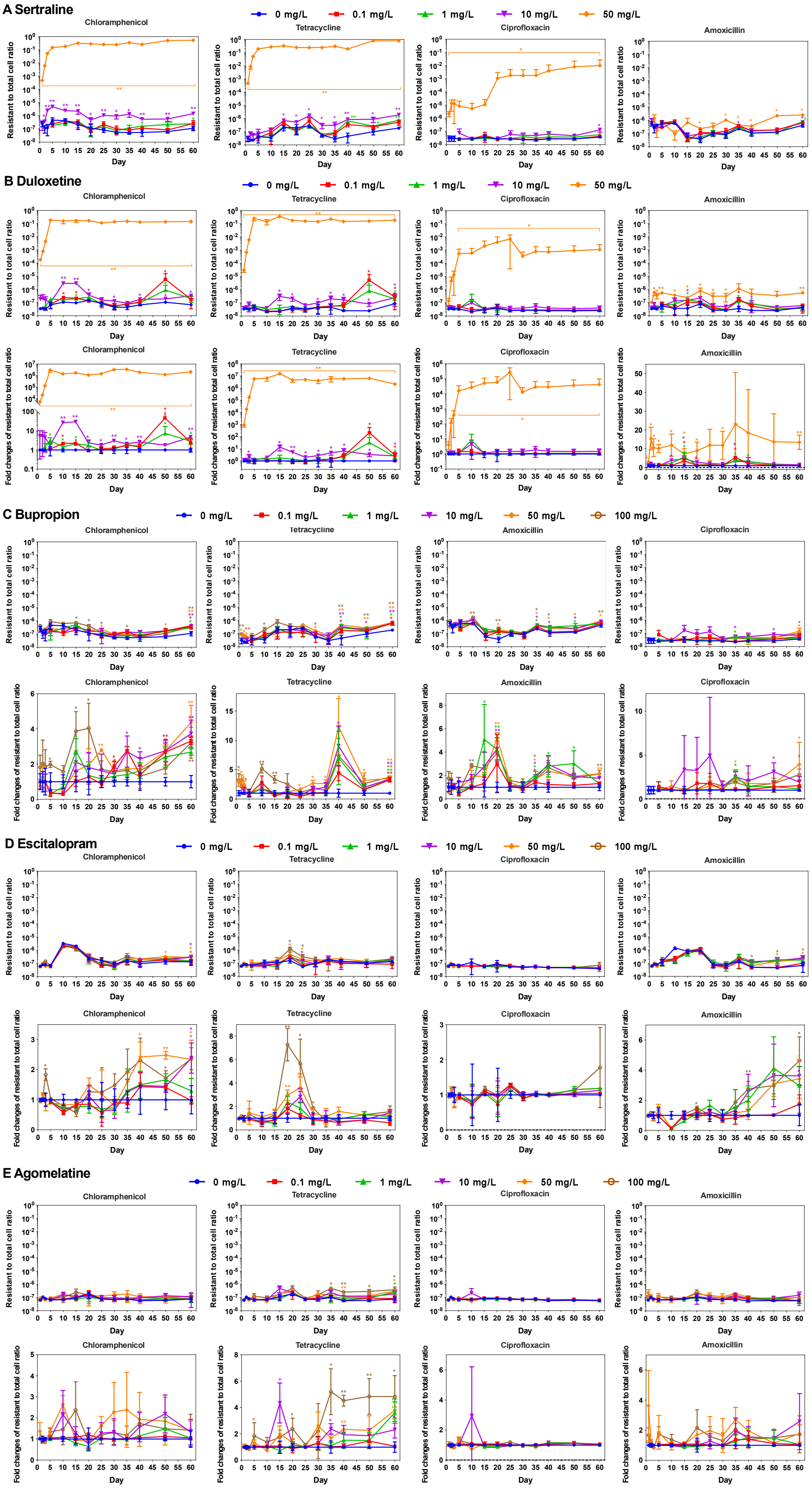

Figure S1. Mutation effects induced by five antidepressants on chloramphenicol-, tetracycline-, ciprofloxacin-, and amoxicillin- selective plates. Data are shown as mean ± SD, n=3 independent experiments. Significant differences between antidepressant-dosed samples and the non-antidepressant control are analyzed by independent-sample *t*-test with Benjamini–Hochberg multiple comparison testing, * $P < 0.05$, ** $P < 0.01$.

Figure S2. Fold changes of minimum inhibition concentrations (MIC) of randomly-picked mutant strains towards multiple antibiotics comparing with the wild-type control. MIC refers to the MIC of the mutant strains; MIC-D5 refers to the MIC of the same randomly-picked mutant strain after cultivating in LB broth for a consecutive 5 days. Data are shown as mean ± SD, n=3 independent experiments.

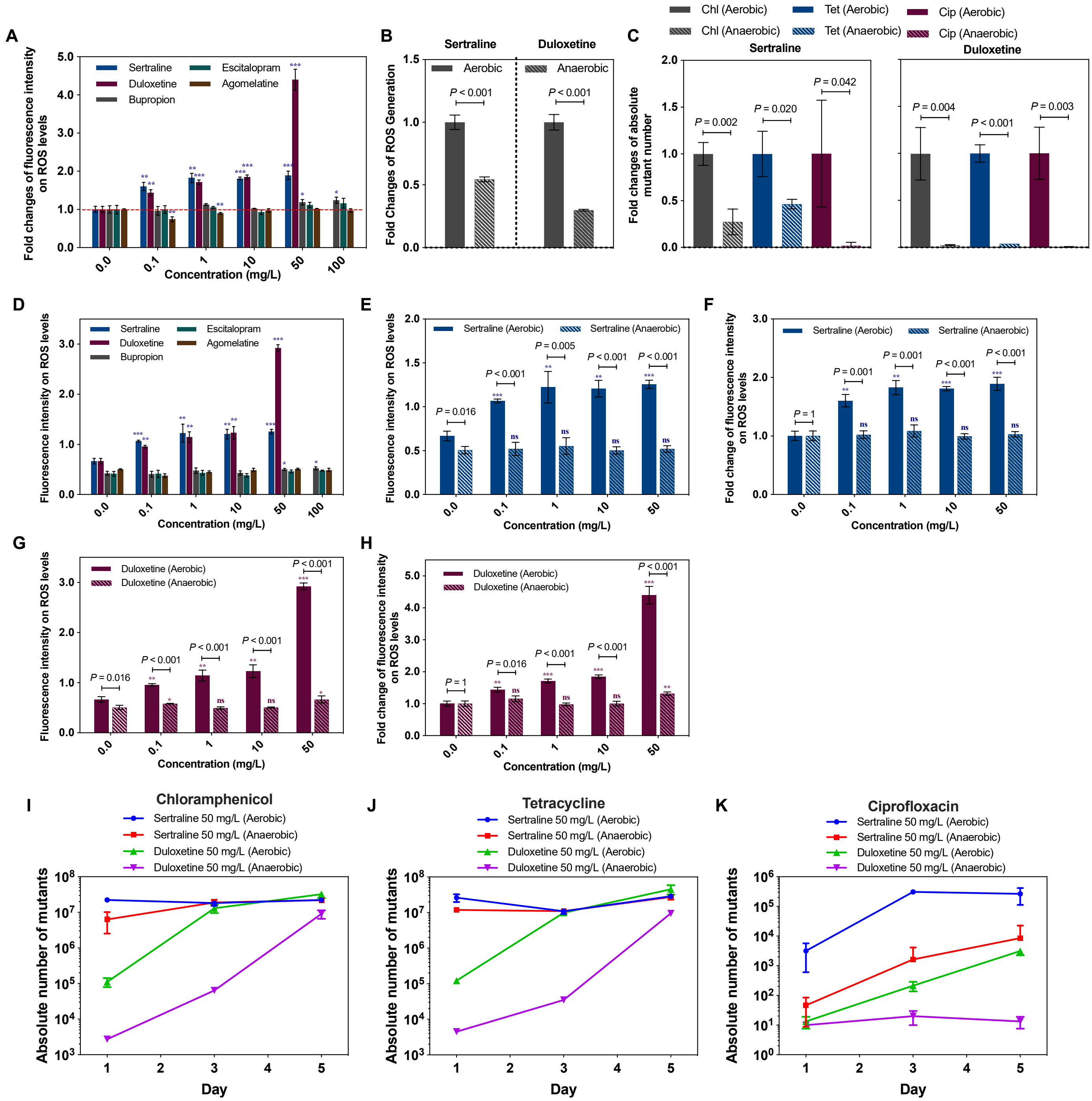

Figure S3. Antidepressants enhance ROS generation level, and thus induce multidrug resistance. (A) Fold changes of ROS generation under aerobic condition. (B) Fold changes of ROS generation under either aerobic or anaerobic conditions (with 50 mg/L sertraline and duloxetine). (C) Fold changes of absolute mutant number on chloramphenicol-, tetracycline-, ciprofloxacin- selective plates, under either aerobic or anaerobic conditions (with 50 mg/L sertraline and duloxetine). (D) ROS generation under the exposure of five antidepressants. (E) ROS generation caused by antidepressant sertraline under both aerobic and anaerobic conditions. (F) Fold changes of ROS generation caused by antidepressant sertraline under both aerobic and anaerobic conditions. (G) ROS generation caused by antidepressant duloxetine under both aerobic and anaerobic conditions. (H) Fold changes of ROS generation caused by antidepressant duloxetine under both aerobic and anaerobic conditions. (I) Absolute mutant numbers on chloramphenicol- selective plate, under the exposure of 50 mg/L sertraline or duloxetine aerobically/anaerobically. (J) Absolute mutant numbers on tetracycline- selective plate, under the exposure of 50 mg/L sertraline or duloxetine aerobically/anaerobically. (K) Absolute mutant numbers on ciprofloxacin- selective plate, under the exposure of 50 mg/L sertraline or duloxetine aerobically/anaerobically. Data are shown as mean ± SD, n=3 independent experiments. Significant differences between antidepressant-dosed samples and the non-antidepressant control are analyzed by independent-sample *t*-test with Benjamini–Hochberg multiple comparison testing, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

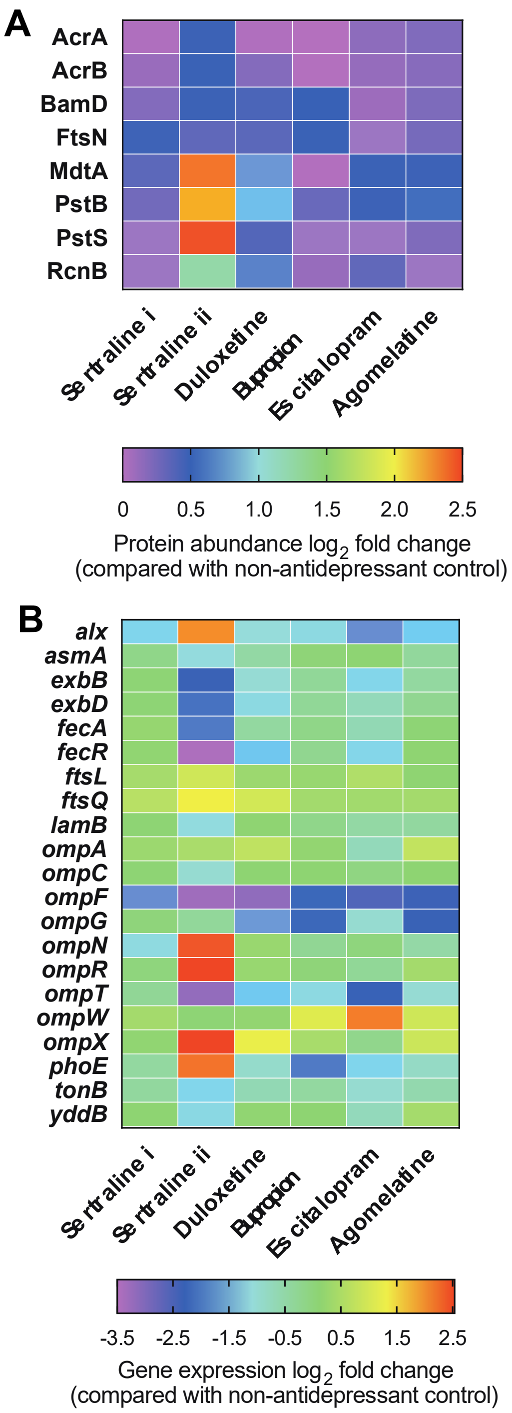

Figure S4. Antidepressants stimulate efflux pump and affect bacterial membrane. (A) Heatmap with $\log_2$ fold changes of key proteins related to efflux pump, resistance-nodulation-division (RND) type efflux pumps, ATP-binding cassette (ABC) superfamily and multi antimicrobial extrusion protein family (MATE). (B) Heatmap with $\log_2$ fold changes of key genes related to bacterial membrane. Sertraline i refers to 1 mg/L, and sertraline ii refers to 50 mg/L. The other four antidepressants are 50 mg/L.

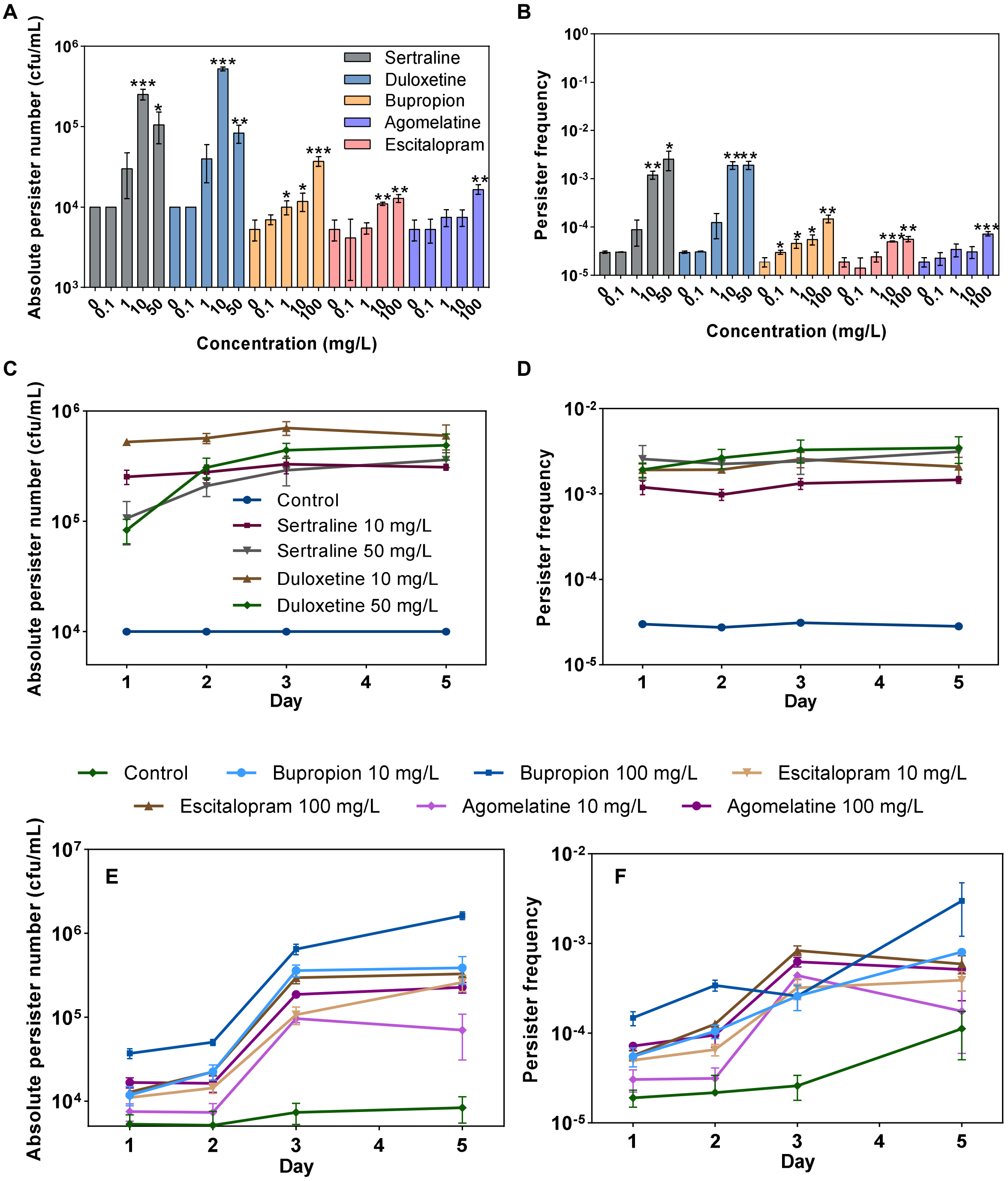

Figure S5. Antidepressants can enhance bacterial persistence towards antibiotic ciprofloxacin. (A) Absolute persister number when exposing wild-type *E. coli* to five antidepressants for 1 day. (B) Ratio of persister number to total cell number when exposing wild-type *E. coli* to five antidepressants for 1 day. (C) Absolute persister number when exposing wild-type *E. coli* to sertraline or duloxetine for a consecutive 5 days. (D) Ratio of persister number to total cell number when exposing wild-type *E. coli* to sertraline or duloxetine for a consecutive 5 days. (E) Absolute persister number when exposing wild-type *E. coli* to bupropion, escitalopram, or agomelatine for a consecutive 5 days. (F) Ratio of persister number to total cell number when exposing wild-type *E. coli* to bupropion, escitalopram, or agomelatine for a consecutive 5 days.

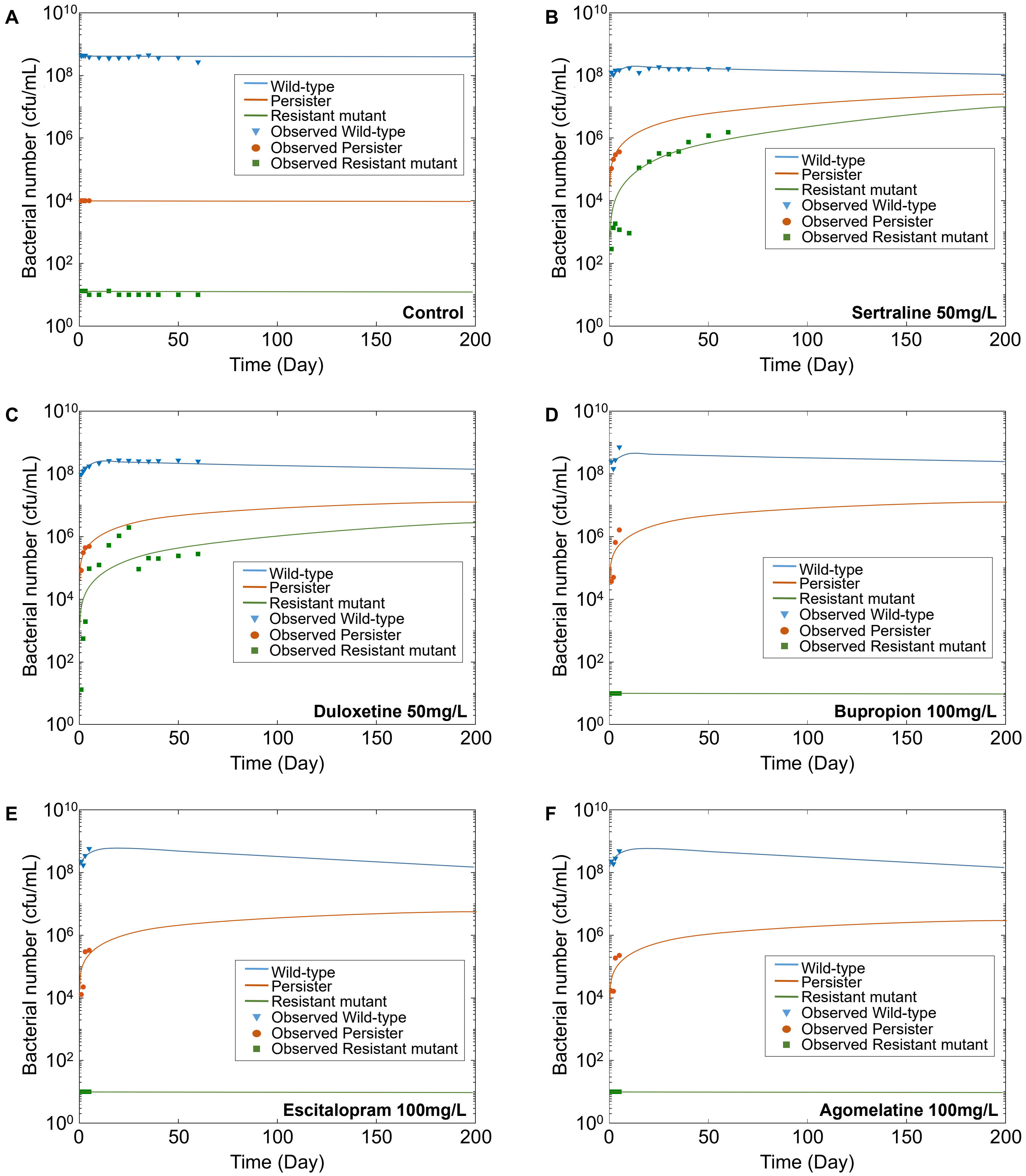

Figure S6. Antidepressants could affect the evolution of persister and resistant bacteria. (A)-(F), simulated trajectories of wild-type, persister, and antibiotic resistant mutant numbers under the non-antidepressant condition, 50 mg/L sertraline, 50 mg/L duloxetine, 100 mg/L bupropion, 100 mg/L escitalopram, and 100 mg/L agomelatine, respectively.

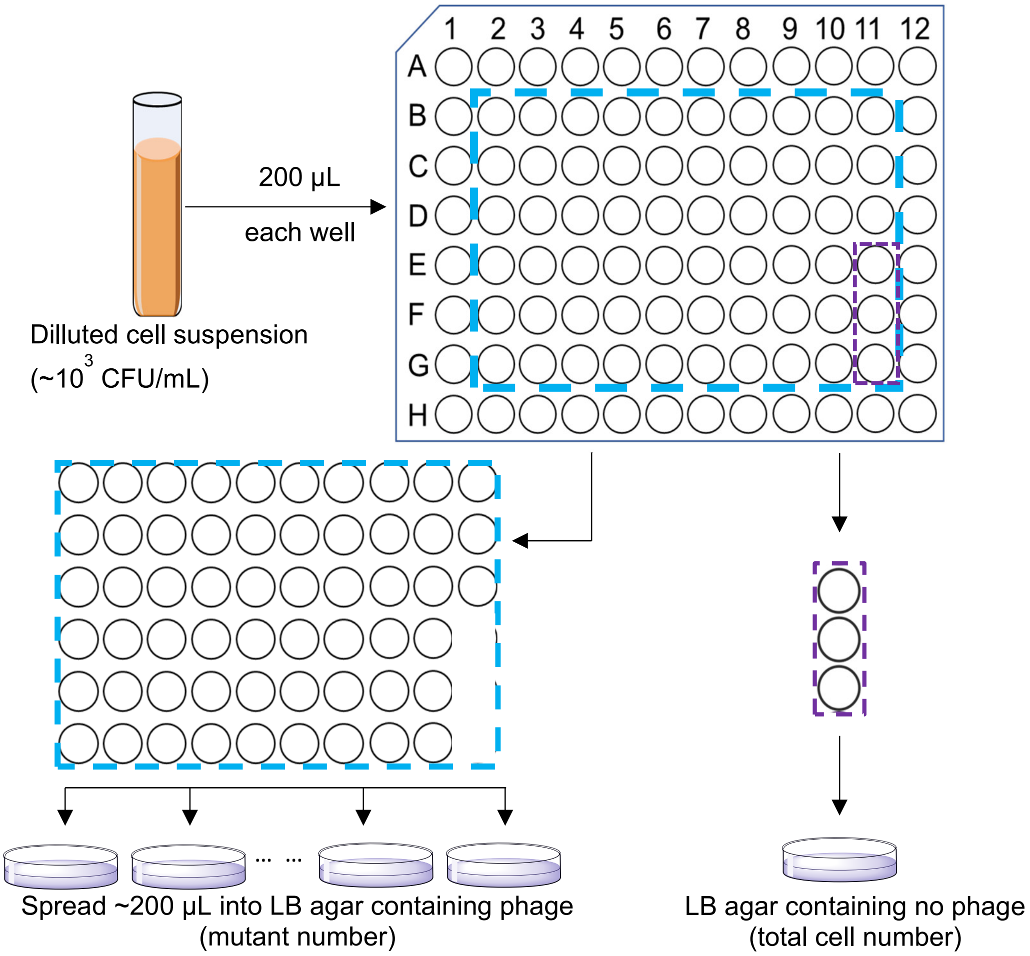

Figure S7. Diagram of fluctuation test

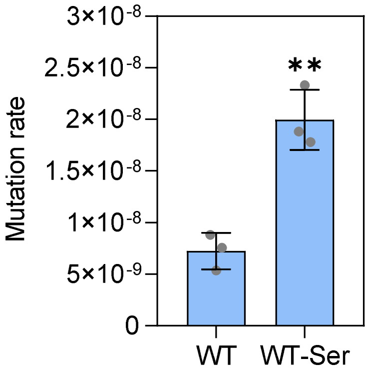

Figure S8. The calculated mutation rate of wild type *E. coli* MG1655 with (WT-Ser) or without (WT) 10 mg/L sertraline treatment. Each sample was run in three replicates. Significant difference between antidepressant-dosed samples and the non-antidepressant control is analyzed by independent-sample *t*-test with Benjamini–Hochberg multiple comparison testing, * $p < 0.05$, ** $p < 0.01$. The zero class of Poisson distribution (P_0) was verified by the range (0.3~2.3) of the expected number of mutations (1).

Supplementary Tables

Table S1 Heredity test of minimum inhibition concentrations (MICs) towards multiple antibiotics when comparing the mutants with the wild-type control

Mutant Strain	MIC*	**Amoxicillin**	**Ampicillin**	**Cephalexin**	**Chloramphenicol**	**Ciprofloxacin**	**Colistin**	**Erythromycin**	**Kanamycin**	**Levofloxacin**	**Norfloxacin**	**Roxithromycin**	**Tetracycline**	**Trimethoprim**
Sertraline 50 mg/L -D1-Chl	MIC	1±0	2.7±0.9	3.0±1.4	13.3±3.8	16±0	1±0	2±0	1.3±0.5	64±0	16±0	2±0	32±0	8±0
	$\text{MIC}_{\text{-D5}}$	1±0	2.7±0.9	3.0±1.4	10.7±3.8	21.3±7.5	1±0	2±0	1±0	64±0	16±0	2±0	42.7±15.1	8±0
Sertraline 50 mg/L -D1-Tet	MIC	2±0	3.3±0.9	2.3±1.2	16±0	6.7±1.9	1±0	2±0	3.3±0.9	8±0	8±0	2±0	26.7±7.5	4±0
	$\text{MIC}_{\text{-D5}}$	2±0	3.3±0.9	2.3±1.2	16±0	5.3±1.9	1±0	2±0	2±0	8±0	8±0	2±0	32±0	3.3±0.9
Sertraline 50 mg/L -D1-Cip	MIC	1.7±0.5	4.7±2.5	5.3±1.9	13.3±3.8	8±0	1.7±0.5	2±0	2±0	8±0	6.7±1.9	2±0	32±0	8±0
	$\text{MIC}_{\text{-D5}}$	1.7±0.5	3.3±0.9	5.3±1.9	16±0	9.3±5.0	1.3±0.5	2±0	1.7±0.5	18.7±10.0	8±0	2±0	16±0	10.7±3.8
Sertraline 50 mg/L -D30-Amo	MIC	2.7±0.9	3.3±0.9	1±0	8.7±5.7	8.0±5.7	1.3±0.5	2±0	1±0	13.3±3.8	8±0	2±0	10.7±3.8	8±0
	$\text{MIC}_{\text{-D5}}$	3.3±0.9	3.3±0.9	1±0	10.7±3.8	6.7±1.9	1.3±0.5	2±0	1±0	16±0	8±0	2±0	8±0	8±0
Sertraline 50 mg/L -D60-Chl	MIC	1.3±0.5	2.7±0.9	5.3±1.9	13.3±3.8	16±0	1±0	2±0	1.3±0.5	64±0	16±0	2±0	32±0	8±0
	$\text{MIC}_{\text{-D5}}$	1±0	3.3±0.9	5.3±1.9	10.7±3.8	21.3±7.5	1±0	2±0	1±0	53.3±15.1	21.3±7.5	2±0	32±0	10.7±3.8
Sertraline 50 mg/L -D60-Tet	MIC	2±0	4±0	3.0±1.4	16±0	8±0	1±0	2±0	3.3±0.9	8±0	8±0	2±0	26.7±7.5	4±0
	$\text{MIC}_{\text{-D5}}$	1.7±0.5	5.3±1.9	3.0±1.4	13.3±3.8	10.7±3.8	1±0	2±0	2.7±0.9	8±0	10.7±3.8	2±0	32±0	4±0
Sertraline 50 mg/L -D60-Cip	MIC	1.7±0.5	5.3±1.9	5.3±1.9	16±0	8±0	1.7±0.5	2±0	2±0	8±0	8±0	2±0	32±0	8±0
	$\text{MIC}_{\text{-D5}}$	2±0	6.7±1.9	5.3±1.9	13.3±3.8	8±0	1.3±0.5	2±0	1.7±0.5	8±0	6.7±1.9	2±0	42.7±15.1	10.7±3.8
Sertraline 50 mg/L -D60-Amo	MIC	3.3±0.9	3.3±0.9	3.0±1.4	8.7±5.7	16±0	1.3±0.5	2±0	1.3±0.5	13.3±3.8	8±0	2±0	13.3±3.8	8±0
	$\text{MIC}_{\text{-D5}}$	3.3±0.9	3.3±0.9	3.0±1.4	6.7±1.9	16±0	1.3±0.5	2±0	1.3±0.5	10.7±3.8	8±0	2±0	10.7±3.8	8±0
Sertraline 1 mg/L -D60-Chl	MIC	1.7±0.5	4.3±2.9	6.7±1.9	16±0	8.0±5.7	1.3±0.5	2±0	1.7±0.5	21.3±7.5	10.7±3.8	2±0	16±0	10.7±3.8
	$\text{MIC}_{\text{-D5}}$	1.3±0.5	4.7±2.5	6.7±1.9	16±0	9.3±5.0	1.3±0.5	2±0	1.7±0.5	18.7±10.0	8±0	2±0	16±0	10.7±3.8
Sertraline 1 mg/L -D60-Tet	MIC	1.7±0.5	4.7±2.5	2.3±1.2	10.7±3.8	6.7±1.9	2.3±1.2	2±0	2.3±1.2	9.3±5.0	5.3±1.9	2±0	21.3±7.5	3.0±1.4
	$\text{MIC}_{\text{-D5}}$	1.7±0.5	3.3±0.9	2.3±1.2	10.7±3.8	6.0±2.8	2.0±1.4	2±0	2.3±1.2	9.3±5.0	5.3±1.9	2±0	26.7±7.5	3.3±0.9
Sertraline 10 mg/L -D60-Cip	MIC	2.7±0.9	8±0	4±0	16±0	13.3±3.8	3.3±0.9	2±0	4±0	10.7±3.8	10.7±3.8	2±0	32±0	8±0
	$\text{MIC}_{\text{-D5}}$	2.7±0.9	8±0	4±0	13.3±3.8	13.3±3.8	2.3±1.2	2±0	2.7±0.9	10.7±3.8	10.7±3.8	2±0	26.7±7.5	8±0
Sertraline 1 mg/L -D60-Amo	MIC	3.3±0.9	6.7±1.9	2.7±0.9	6.0±2.8	8±0	1±0	1.7±0.5	1.3±0.5	6.7±1.9	4±0	2±0	8±0	4±0
	$\text{MIC}_{\text{-D5}}$	4±0	6.7±1.9	2.7±0.9	4.7±2.5	8±0	1±0	1.7±0.5	1.3±0.5	6.0±2.8	3.3±0.9	2±0	8±0	4±0
Duloxetine 50 mg/L -D60-Chl	MIC	1.3±0.5	4±0	8±0	32±0	32±0	1±0	2±0	1.7±0.5	64±0	6.7±1.9	2±0	42.7±15.1	10.7±3.8
	$\text{MIC}_{\text{-D5}}$	1.3±0.5	5.3±1.9	8±0	32±0	26.7±7.5	1±0	2±0	1±0	64±0	5.3±1.9	2±0	53.3±15.1	8±0
Duloxetine 50 mg/L -D60-Tet	MIC	2±0	5.3±1.9	6.7±1.9	16±0	32±0	2±0	2±0	4±0	32±0	6.7±1.9	2±0	42.7±15.1	16±0
	$\text{MIC}_{\text{-D5}}$	2±0	5.3±1.9	6.7±1.9	13.3±3.8	32±0	2±0	2±0	2.7±0.9	26.7±7.5	10.7±3.8	2±0	42.7±15.1	16±0
Duloxetine 50 mg/L -D60-Cip	MIC	2±0	6.7±1.9	6.7±1.9	32±0	42.7±15.1	1.7±0.5	2±0	4±0	64±0	5.3±1.9	2±0	64±0	16±0
	$\text{MIC}_{\text{-D5}}$	2.7±0	5.3±1.9	6.7±1.9	26.7±7.5	42.7±15.1	1.3±0.5	2±0	4±0	53.3±15.1	3.3±0.9	2±0	53.3±15.1	13.3±3.8
Duloxetine 50 mg/L -D60-Amo	MIC	2.7±0.9	13.3±3.8	8±0	26.7±7.5	32±0	1.3±0.5	2±0	2±0	64±0	8±0	2±0	64±0	16±0
	$\text{MIC}_{\text{-D5}}$	4.0±2.8	10.7±3.8	8±0	21.3±7.5	32±0	1.3±0.5	2±0	2.3±1.2	64±0	10.7±3.8	2±0	53.3±15.1	13.3±3.8
	MIC	1±0	2.7±0.9	6.7±1.9	21.3±7.5	32±0	1.3±0.5	2±0	2±0	64±0	5.3±1.9	2±0	53.3±15.1	16±0

Mutant Strain	MIC*	**Amoxicillin**	**Ampicillin**	**Cephalexin**	**Chloramphenicol**	**Ciprofloxacin**	**Colistin**	**Erythromycin**	**Kanamycin**	**Levofloxacin**	**Norfloxacin**	**Roxithromycin**	**Tetracycline**	**Trimethoprim**
Duloxetine 50 mg/L -D1-Chl	MIC$_{-D5}$	1±0	3.3±0.9	6.7±1.9	26.7±7.5	32±0	1.3±0.5	2±0	1.3±0.5	64±0	4±0	2±0	42.7±15.1	21.3±7.5
Duloxetine 50 mg/L -D1-Tet	MIC	2±0	6.7±1.9	8±0	21.3±7.5	32±0	2±0	2±0	3.3±0.9	64±0	5.3±1.9	2±0	64±0	16±0
	MIC$_{-D5}$	2±0	2.7±0.9	8±0	21.3±7.5	26.7±7.5	1.7±0.5	2±0	3.0±1.4	53.3±15.1	5.3±1.9	2±0	64±0	13.3±3.8
Duloxetine 50 mg/L -D5-Cip	MIC	1±0	4±0	2.3±1.2	10.7±3.8	32±0	1±0	2±0	2.7±0.9	32±0	2.7±0.9	2±0	21.3±7.5	13.3±3.8
	MIC$_{-D5}$	1±0	4±0	2.3±1.2	9.3±5.0	53.3±15.1	1±0	2±0	2.3±1.2	32±0	3.3±0.9	2±0	21.3±7.5	10.7±3.8
Duloxetine 1 mg/L -D60-Chl	MIC	1.7±0.5	4±0	6.7±1.9	42.7±15.1	26.7±7.5	1.3±0.5	2±0	2±0	53.3±15.1	5.3±1.9	2±0	37.3±20	5.3±1.9
	MIC$_{-D5}$	1.3±0.5	3.3±0.9	6.7±1.9	53.3±15.1	32±0	1.3±0.5	2±0	1.7±0.5	42.7±15.1	5.3±1.9	2±0	42.7±15.1	4±0
Duloxetine 1 mg/L -D60-Tet	MIC	2±0	6.7±1.9	9.3±5.0	21.3±7.5	32±0	2±0	1.7±0.5	3.3±0.9	26.7±7.5	4.7±2.5	2±0	53.3±15.1	10.7±3.8
	MIC$_{-D5}$	1.7±0.5	5.3±1.9	9.3±5.0	18.7±10.0	26.7±7.5	2±0	1.7±0.5	2.3±1.2	32±0	3.3±0.9	2±0	42.7±15.1	8±0
Bupropion 100 mg/L -D60- Chl	MIC	1±0	2.7±0.9	4±0	21.3±7.5	16±0	1.3±0.5	2±0	1.7±0.5	64±0	8±0	2±0	16±0	8±0
	MIC$_{-D5}$	1±0	3.3±0.9	4±0	16±0	16±0	1±0	2±0	1.3±0.5	42.7±15.1	10.7±3.8	2±0	32±0	10.7±3.8
Bupropion 100 mg/L -D60- Tet	MIC	1.7±0.5	4.7±2.5	4±0	13.3±3.8	16±0	1.3±0.5	2±0	2.7±0.9	32±0	6.7±1.9	2±0	32±0	8±0
	MIC$_{-D5}$	1.3±0.5	4.0±2.8	4±0	10.7±3.8	13.3±3.8	1.3±0.5	2±0	1.3±0.5	42.7±15.1	10.7±3.8	2±0	32±0	10.7±3.8
Bupropion 100 mg/L -D60-Amo	MIC	3.3±0.9	4±0	2.0±1.4	4.0±2.8	9.3±5.0	1±0	2±0	1.3±0.5	13.3±13.2	4.0±2.8	1.3±0.5	18.7±10.0	6.7±1.9
	MIC$_{-D5}$	2.7±0.9	3.3±0.9	2.0±1.4	4.7±2.5	8±0	1±0	2±0	1.3±0.5	5.3±1.9	3.3±0.9	1.3±0.5	10.7±3.8	5.3±1.9

* MIC refers to the MIC of the randomly picked mutant strains; MIC$_{-D5}$ refers to the MIC of the same randomly-selected mutant strain after cultivating in LB broth for a consecutive 5 days. Data are shown as mean ± SD, n=3 independent experiments.

Table S2 Genes related to ROS production in *E. coli* MG1655 after exposure of antidepressants

Gene	**COG Annotation**	**Log$_2$ Fold Change of FPKM** *					
		Sertraline 1 mg/L	**Sertraline 50 mg/L**	**Duloxetine 50 mg/L**	**Bupropion 50 mg/L**	**Escitalopram 50 mg/L**	**Agomelatine 50 mg/L**
ahpF	alkyl hydroperoxide reductase FAD/NAD(P)-binding	0.78	1.02	0.35	0.88	0.79	0.76
alkB	oxidative demethylase of N1-methyladenine or N3-methylcytosine DNA lesions	0.54	0.64	0.42	1.07	1.01	1.25
dps	Fe-binding and storage protein stress-inducible DNA-binding protein	1.65	0.60	1.42	1.61	0.81	2.00
glyS	glycine tRNA synthetase beta subunit	-0.53	1.23	-0.06	-0.25	0.50	-0.17
gor	glutathione oxidoreductase	-0.08	0.36	0.47	0.00	-0.08	0.15
hcp	hybrid-cluster [4Fe-2S-2O] subunit of anaerobic terminal reductases	2.20	2.14	1.92	1.79	0.41	2.35
hcr	HCP oxidoreductase NADH-dependent	1.56	1.79	2.00	1.00	0.79	1.63
iraD	RpoS stabilzer after DNA damage anti-RssB factor	0.25	2.61	1.16	1.64	0.59	0.62
iraP	anti-RssB factor RpoS stabilzer during Pi starvation anti-adapter protein	-1.92	-1.59	-2.76	-1.72	-1.07	-2.20
iscR	isc operon transcriptional repressor suf operon transcriptional activator oxidative stress- and iron starvation-inducible autorepressor	-0.44	-0.71	-1.33	-0.21	-0.11	-0.51
katE	catalase HPII heme d-containing	0.27	6.10	2.24	0.17	0.47	-0.52
katG	catalase-peroxidase HPI heme b-containing	0.35	0.76	1.59	0.31	0.57	0.07
lysR	transcriptional activator of lysA autorepressor	-0.11	-0.85	-0.22	0.60	-0.05	1.19
oxyR	oxidative and nitro sative stress transcriptional regulator	0.47	0.49	0.21	-0.40	-0.48	-0.44
rutA	pyrimidine oxygenase FMN-dependent	0.68	2.57	1.59	0.55	0.77	1.02

Gene	**COG Annotation**	**Log$_2$ Fold Change of FPKM** [*]					
		Sertraline 1 mg/L	**Sertraline 50 mg/L**	**Duloxetine 50 mg/L**	**Bupropion 50 mg/L**	**Escitalopram 50 mg/L**	**Agomelatine 50 mg/L**
rutD	putative reactive intermediate detoxifying amino acrylate hydrolase	1.81	0.93	0.86	2.21	-0.01	2.40
sodB	superoxide dismutase%2C Fe	0.53	1.33	0.83	0.31	0.28	0.77
sodC	superoxide dismutase%2C Cu Zn periplasmic	0.00	2.58	0.91	0.73	0.95	0.97
soxR	redox-sensitive transcriptional activator of soxS autorepressor	0.84	0.54	1.21	1.33	1.34	1.54
soxS	superoxide response regulon transcriptional activator autoregulator	-2.28	2.87	-0.02	-0.90	-0.79	-2.23
sufA	Fe-S cluster assembly protein	2.71	1.88	2.61	2.25	2.03	2.44
ydeI	hydrogen peroxide resistance OB fold protein putative periplasmic protein	0.14	2.72	0.21	0.04	0.39	-0.99
ydeJ	inactive PncC family protein	0.01	3.20	0.59	-0.39	0.22	-0.12
ydeO	UV-inducible global regulator EvgA-GadE-dependent	0.17	3.02	1.34	-0.26	-0.29	0.06
yggE	oxidative stress defense protein	0.44	0.86	0.84	0.28	-1.10	-0.83
yhhZ	putative Hcp1 family polymorphic toxin protein putative colicin-like DNase/tRNase activity	0.33	3.04	1.02	0.62	0.01	-0.86

[*]: Comparing with the non-antidepressant control group

Table S3 Proteins related to ROS production in *E. coli* MG1655 after exposure of antidepressants

Protein	**Description**	**Log$_2$ Fold Change of Protein Abundance** *					
		Sertraline 1 mg/L	**Sertraline 50 mg/L**	**Duloxetine 50 mg/L**	**Bupropion 50 mg/L**	**Escitalopram 50 mg/L**	**Agomelatine 50 mg/L**
AhpF	Alkyl hydroperoxide reductase subunit F	-0.08	0.21	0.04	-0.08	0.02	0.03
Gor	Glutathione reductase	-0.04	0.27	0.16	-0.02	0.13	0.16
Hcp	Hydroxylamine reductase	0.43	0.77	0.68	0.12	0.50	0.47
Hcr	NADH oxidoreductase	0.95	1.23	0.05	0.55	-0.01	0.02
KatE	Catalase HPII	0.98	2.90	1.05	0.34	1.15	0.39
LysC	Lysine-sensitive kinase	0.14	1.30	0.76	0.34	0.57	0.10
LysS	Lysine--tRNA ligase	0.09	0.08	0.07	0.16	0.09	0.13
OxyR	Hydrogen peroxide-inducible genes activator	0.36	0.69	0.31	0.22	0.49	0.06
SodA	Superoxide dismutase [Mn]	0.17	0.70	0.68	0.23	-0.17	0.13
SodB	Superoxide dismutase [Fe]	0.04	0.42	0.22	0.09	-0.09	-0.07
YajD	Putative HNH nuclease	3.05	1.43	3.97	3.00	1.11	0.40
YggE	Oxidative stress defense protein	0.09	0.89	0.57	0.17	0.58	0.10

*: Comparing with the non-antidepressant control group

Table S4 Genes related to ROS production in antidepressant sertraline- induced (60 days) mutants, after the exposure of 50 mg/L sertraline

Gene	**COG Annotation**	**Log_2 Fold Change of FPKM** *							
		Sertraline 1 mg/L-chloramphenicol	**Sertraline 1 mg/L-tetracycline**	**Sertraline 1 mg/L-ciprofloxacin**	**Sertraline 1 mg/L-amoxicillin**	**Sertraline 50 mg/L-chloramphenicol**	**Sertraline 50 mg/L-tetracycline**	**Sertraline 50 mg/L-ciprofloxacin**	**Sertraline 50 mg/L-amoxicillin**
ahpF	alkyl hydroperoxide reductase FAD/NAD(P)-binding	1.47	1.31	1.43	0.83	1.08	0.71	1.16	1.18
alkB	oxidative demethylase of N1-methyladenine or N3-methylcytosine DNA lesions	-0.58	0.21	0.45	-0.82	-0.44	0.10	-0.98	-0.46
dps	Fe-binding and storage protein stress-inducible DNA-binding protein	0.42	1.55	1.28	0.86	0.36	0.94	1.10	0.39
glyS	glycine tRNA synthetase beta subunit	1.39	1.47	1.03	1.02	1.33	0.73	1.04	1.52
gor	glutathione oxidoreductase	0.57	0.70	0.68	1.32	0.50	0.61	0.71	0.39
hcp	hybrid-cluster [4Fe-2S-2O] subunit of anaerobic terminal reductases	-0.37	2.23	1.00	0.33	0.42	0.76	1.33	0.63
hcr	HCP oxidoreductase NADH-dependent	0.94	1.96	1.50	1.11	1.18	1.40	1.63	0.82
iraD	RpoS stabilzer after DNA damage anti-RssB factor	2.05	2.35	2.07	2.46	1.81	0.36	1.87	0.84
iraP	anti-RssB factor RpoS stabilzer during Pi starvation anti-adapter protein	-3.57	-2.06	-2.99	-1.60	-1.83	-2.02	-1.77	-2.17
iscR	isc operon transcriptional repressor suf operon transcriptional activator oxidative stress- and iron starvation-inducible autorepressor	0.08	-0.08	-0.05	0.57	0.69	-0.40	-0.04	0.22
katE	catalase HPII heme d-containing	4.40	4.02	2.01	2.95	0.86	1.32	2.07	1.31
katG	catalase-peroxidase HPI heme b-containing	1.21	1.14	1.07	2.03	1.57	1.25	1.97	1.12

Gene	COG Annotation	Log$_2$ Fold Change of FPKM *							
		Sertraline 1 mg/L-chloramphenicol	**Sertraline 1 mg/L-tetracycline**	**Sertraline 1 mg/L-ciprofloxacin**	**Sertraline 1 mg/L-amoxicillin**	**Sertraline 50 mg/L-chloramphenicol**	**Sertraline 50 mg/L-tetracycline**	**Sertraline 50 mg/L-ciprofloxacin**	**Sertraline 50 mg/L-amoxicillin**
lysR	transcriptional activator of lysA autorepressor	-0.76	-0.51	0.01	-0.82	-0.44	0.19	-0.59	-0.68
oxyR	oxidative and nitro sative stress transcriptional regulator	0.49	0.84	0.91	1.12	0.57	0.80	-0.21	0.46
rutA	pyrimidine oxygenase FMN-dependent	1.69	1.89	1.47	2.15	0.70	0.98	1.80	0.38
rutD	putative reactive intermediate detoxifying amino acrylate hydrolase	1.37	0.51	0.19	2.34	1.41	0.99	1.83	0.32
sodB	superoxide dismutase%2C Fe	0.79	0.68	0.64	0.57	0.88	0.41	0.46	0.52
sodC	superoxide dismutase%2C Cu Zn periplasmic	2.00	1.94	1.10	2.01	0.03	1.25	0.85	0.42
soxR	redox-sensitive transcriptional activator of soxS autorepressor	-1.33	-1.62	0.40	0.49	0.06	0.65	0.12	-0.34
soxS	superoxide response regulon transcriptional activator autoregulator	0.05	0.42	1.20	2.35	1.02	0.55	1.04	0.71
sufA	Fe-S cluster assembly protein	-0.27	0.34	-0.58	-0.03	-0.81	-0.91	0.38	-1.41
ydeI	hydrogen peroxide resistance OB fold protein putative periplasmic protein	2.40	2.23	0.68	2.40	-0.11	0.70	1.32	0.56
ydeJ	inactive PncC family protein	2.68	1.44	0.93	3.57	0.78	1.24	1.07	0.43
ydeO	UV-inducible global regulator EvgA- GadE-dependent	0.90	-1.41	-1.42	0.95	-0.88	0.55	0.18	-1.02
yggE	oxidative stress defense protein	1.21	1.36	0.47	1.42	0.22	0.33	0.54	-0.18
yhhZ	putative Hcp1 family polymorphic toxin protein	0.33	0.67	0.89	2.35	0.64	0.62	-0.36	-0.17

Gene	**COG Annotation**	**Log_2 Fold Change of FPKM** *							
		Sertraline 1 mg/L-chloramphenicol	**Sertraline 1 mg/L-tetracycline**	**Sertraline 1 mg/L-ciprofloxacin**	**Sertraline 1 mg/L-amoxicillin**	**Sertraline 50 mg/L-chloramphenicol**	**Sertraline 50 mg/L-tetracycline**	**Sertraline 50 mg/L-ciprofloxacin**	**Sertraline 50 mg/L-amoxicillin**
	putative colicin-like DNase/tRNase activity								

*: Comparing with the mutant control group without any sertraline dosage

Table S5 Proteins related to ROS production in antidepressant sertraline- induced (60 days) mutants, after the exposure of 50 mg/L sertraline

Protein	Description	Log$_2$ Fold Change of FPKM *							
		Sertraline 1 mg/L-chloramphenicol	**Sertraline 1 mg/L-tetracycline**	**Sertraline 1 mg/L-ciprofloxacin**	**Sertraline 1 mg/L-amoxicillin**	**Sertraline 50 mg/L-chloramphenicol**	**Sertraline 50 mg/L-tetracycline**	**Sertraline 50 mg/L-ciprofloxacin**	**Sertraline 50 mg/L-amoxicillin**
AhpF	Alkyl hydroperoxide reductase subunit F	0.24	-0.12	0.12	0.42	-0.37	-0.20	-0.38	0.15
Gor	Glutathione reductase	-0.01	-0.25	0.04	0.35	-0.23	-0.31	-0.89	0.25
Hcp	Hydroxylamine reductase	-1.49	-0.09	1.25	-1.65	0.19	0.97	0.52	-1.43
Hcr	NADH oxidoreductase	0.06	-0.01	0.45	-0.85	0.43	0.99	1.76	-0.60
KatE	Catalase HPII	1.18	1.43	-0.15	1.41	-0.31	0.10	-0.70	0.77
LysC	Lysine-sensitive kinase	3.18	0.73	0.50	3.83	0.46	2.99	0.84	3.32
LysS	Lysine--tRNA ligase	0.38	0.08	-0.06	0.69	0.02	0.09	-0.33	0.12
OxyR	Hydrogen peroxide-inducible genes activator	0.17	-0.44	0.00	0.44	-0.58	-0.23	-1.49	0.03
SodA	Superoxide dismutase [Mn]	0.58	0.91	-0.13	-0.93	-0.68	-0.78	-1.71	-1.22
SodB	Superoxide dismutase [Fe]	-0.04	0.21	-0.13	-0.15	0.00	0.00	0.03	0.78
YajD	Putative HNH nuclease	-0.23	0.52	0.30	0.53	-0.25	0.31	-0.64	1.52
YggE	Oxidative stress defense protein	1.40	0.73	0.73	1.55	0.20	1.21	0.10	1.31

*: Comparing with the mutant control group without any sertraline dosage

Table S6 Genes related to efflux pump in *E. coli* MG1655 after exposure of antidepressants

Gene	**COG Annotation**	**Log$_2$ Fold Change of FPKM** *					
		Sertraline 1 mg/L	**Sertraline 50 mg/L**	**Duloxetine 50 mg/L**	**Bupropion 50 mg/L**	**Escitalopram 50 mg/L**	**Agomelatine 50 mg/L**
acrA	multidrug efflux system	0.29	2.20	0.10	-0.70	-0.64	-0.89
acrB	multidrug efflux system protein	0.03	2.66	0.48	-0.10	0.17	-0.09
acrD	aminoglycoside/multidrug efflux system	0.62	2.50	0.80	-0.77	-0.68	-0.68
acrR	transcriptional repressor	-1.08	-0.22	-1.23	-0.98	-2.08	-1.72
bamA	BamABCDE complex OM biogenesis outer membrane pore-forming assembly factor	-0.12	1.12	0.05	0.02	0.37	-0.14
cusC	copper/silver efflux system outer membrane component	1.35	-1.39	0.70	0.87	1.21	1.08
emrA	multidrug efflux system	0.10	0.88	-1.20	-0.13	-0.96	-0.25
emrB	multidrug efflux system protein	0.18	1.45	0.91	-0.45	-0.73	-0.18
ftsX	putative ABC transporter permease	0.37	0.88	0.04	0.14	-0.08	0.54
iceT	putative citrate/iron-citrate/zinc-citrate efflux transporter	0.33	4.06	1.22	-0.15	0.53	0.57
macB	macrolide ABC transporter peremase/ATPase	1.06	0.51	1.14	0.63	-0.25	1.48
marA	multiple antibiotic resistance transcriptional regulator	-0.07	4.37	0.72	-0.97	-1.55	0.17
mdtA	multidrug efflux system subunit A	0.37	5.65	0.98	-0.16	0.42	-0.45
mdtB	multidrug efflux system subunit B	-0.20	4.86	0.50	0.19	0.21	-0.33
mdtC	multidrug efflux system subunit C	0.40	4.68	0.62	0.02	0.64	-0.13
mdtE	anaerobic multidrug efflux transporter ArcA-regulated	2.00	-3.25	-0.75	1.12	0.02	1.20
mdtF	anaerobic multidrug efflux transporter ArcA-regulated	1.92	-2.51	-0.36	1.59	0.69	1.28
mdtM	multidrug efflux system protein	1.71	2.31	1.26	1.89	0.20	2.05
mlaA	ABC transporter maintaining OM lipid asymmetry OM lipoprotein component	-0.47	1.38	-0.61	-0.68	-0.49	-0.29
mlaB	ABC transporter maintaining OM lipid asymmetry cytoplasmic STAS component	-1.63	3.56	0.51	-0.92	-1.73	-1.52
mlaC	ABC transporter maintaining OM lipid asymmetry periplasmic binding protein	-0.43	2.41	0.48	-0.69	-1.03	-0.30
mlaF	ABC transporter maintaining OM lipid asymmetry ATP-binding protein	-0.22	1.18	0.53	-0.20	-0.43	-0.05

Gene	COG Annotation	Log_2 Fold Change of FPKM [*]					
		Sertraline 1 mg/L	**Sertraline 50 mg/L**	**Duloxetine 50 mg/L**	**Bupropion 50 mg/L**	**Escitalopram 50 mg/L**	**Agomelatine 50 mg/L**
mntP	putative Mn(2+) efflux pump mntR-regulated	0.12	1.25	-0.28	-0.66	-2.06	-1.57
nikB	nickel ABC transporter permease	0.78	0.18	1.66	0.78	0.70	-0.06
oppA	oligopeptide ABC transporter periplasmic binding protein	0.34	1.52	0.45	0.76	1.12	0.32
oppB	oligopeptide ABC transporter permease	0.52	1.89	-1.02	1.37	0.83	0.94
oppC	oligopeptide ABC transporter permease	0.74	1.27	0.82	0.92	1.64	1.08
oppD	oligopeptide ABC transporter ATPase	0.54	1.13	0.33	1.10	1.25	0.92
phnC	phosphonate ABC transporter ATPase	1.23	7.39	0.59	2.36	0.56	0.33
phnD	phosphonate ABC transporter periplasmic binding protein	1.15	5.29	1.66	0.83	-0.39	0.81
pstA	phosphate ABC transporter permease	0.30	5.23	1.11	-0.37	-0.26	-0.06
pstB	phosphate ABC transporter ATPase	-0.73	4.22	-0.09	-0.92	-1.07	-1.24
pstC	phosphate ABC transporter permease	-0.25	5.24	0.72	-0.70	-0.99	-1.30
pstS	phosphate ABC transporter periplasmic binding protein	-0.71	7.48	1.98	-0.66	-1.30	-0.55
rcnB	periplasmic modulator of Ni and Co efflux	-0.94	1.91	1.33	-0.55	-1.01	-1.05
ssuB	aliphatic sulfonate ABC transporter ATPase	0.63	1.03	1.56	0.17	0.93	0.87
tatE	TatABCE protein translocation system subunit	-1.26	1.97	1.22	1.01	1.21	0.78
tolB	periplasmic protein	-0.32	1.06	-0.10	-0.64	-0.81	-0.97
tolC	transport channel	-0.40	0.88	0.01	-0.29	-0.30	-0.46
tolR	membrane spanning protein in TolA-TolQ-TolR complex	0.07	1.76	0.39	0.07	-0.56	-0.54
ybbA	putative ABC transporter ATPase	0.53	3.41	1.02	-0.45	0.03	-0.27
ybbP	putative ABC transporter permease	0.19	2.33	0.64	0.00	0.14	-0.33
ybhS	putative ABC transporter permease	0.93	-1.17	-0.30	1.14	1.53	0.87
yciK	putative EmrKY-TolC system oxoacyl-(acyl carrier protein) reductase	0.15	1.95	0.54	-0.29	-0.84	-0.22
ydhI	DUF1656 family putative inner membrane efflux pump associated protein	1.81	1.99	2.21	2.44	3.43	1.98

[*]: Comparing with the non-antidepressant control group

Table S7 Proteins related to efflux pump in *E. coli* MG1655 after exposure of antidepressants

Protein	Description	Log$_2$ Fold Change of Protein Abundance [*]					
		Sertraline 1 mg/L	**Sertraline 50 mg/L**	**Duloxetine 50 mg/L**	**Bupropion 50 mg/L**	**Escitalopram 50 mg/L**	**Agomelatine 50 mg/L**
AcrA	Multidrug efflux pump subunit	0.02	0.44	0.02	0.00	0.13	0.18
AcrB	Multidrug efflux pump subunit	0.09	0.46	0.17	0.00	0.11	0.16
BamD	Outer membrane protein assembly factor	0.17	0.44	0.36	0.50	0.08	0.19
FtsN	Cell division protein	0.43	0.28	0.30	0.46	-0.13	0.21
MdtA	Multidrug resistance protein	0.30	2.31	0.76	0.01	0.45	0.43
PstB	Phosphate import ATP-binding protein	0.22	2.18	0.85	0.25	0.43	0.61
PstS	Phosphate-binding protein	-0.28	2.42	0.33	-0.29	-0.21	0.18
RcnB	Nickel/cobalt homeostasis protein	-0.02	1.23	0.69	0.10	0.28	-0.20
TolA	Tol-Pal system protein	-0.21	0.24	0.19	-0.49	0.00	-0.10
TolB	Tol-Pal system protein	-0.19	0.03	-0.05	-0.17	-0.04	-0.19
TolC	Outer membrane protein	0.04	-0.21	-0.31	0.13	0.02	0.13
TolQ	Tol-Pal system protein	-0.25	0.03	-0.28	-0.19	0.40	0.73
TolR	Tol-Pal system protein	-0.11	-1.18	-0.91	-0.20	-0.06	-0.23
YciK	Uncharacterized oxidoreductase	-0.38	0.37	0.60	0.24	0.11	-0.16

[*]: Comparing with the non-antidepressant control group

Table S8 Genes related to efflux pump in antidepressant sertraline- induced (60 days) mutants, after the exposure of 50 mg/L sertraline

Gene	**COG Annotation**	**Log$_2$ Fold Change of FPKM** *							
		Sertraline 1 mg/L-chloramphenicol	**Sertraline 1 mg/L-tetracycline**	**Sertraline 1 mg/L-ciprofloxacin**	**Sertraline 1 mg/L-amoxicillin**	**Sertraline 50 mg/L-chloramphenicol**	**Sertraline 50 mg/L-tetracycline**	**Sertraline 50 mg/L-ciprofloxacin**	**Sertraline 50 mg/L-amoxicillin**
acrA	multidrug efflux system	0.15	0.03	-0.01	-0.30	1.11	0.15	0.74	0.94
acrB	multidrug efflux system protein	0.73	0.70	0.42	-0.05	1.30	0.39	1.15	1.47
acrD	aminoglycoside/multidrug efflux system	3.35	1.50	1.47	2.61	1.19	0.98	0.26	0.52
acrR	transcriptional repressor	-0.76	-1.20	0.30	0.14	-0.34	1.24	-0.09	0.13
bamA	BamABCDE complex OM biogenesis outer membrane pore-forming assembly factor	0.90	0.59	0.00	-0.24	0.33	0.10	-0.23	0.35
cusC	copper/silver efflux system outer membrane component	-1.44	-1.30	-0.91	-0.50	-0.25	-0.98	-0.93	-1.05
emrA	multidrug efflux system	-0.44	-0.71	-0.75	-0.38	-0.53	-0.77	-0.96	-0.80
emrB	multidrug efflux system protein	0.43	-0.06	-0.49	0.31	-0.77	-0.57	-0.55	-0.40
ftsX	putative ABC transporter permease	0.88	0.44	-0.02	0.70	-0.17	0.14	0.07	0.03
iceT	putative citrate/iron-citrate/zinc-citrate efflux transporter	3.19	-0.24	-1.15	1.35	0.73	-1.59	0.82	0.93
macB	macrolide ABC transporter peremase/ATPase	2.07	1.47	0.96	2.04	-1.22	1.70	1.26	0.59
marA	multiple antibiotic resistance transcriptional regulator	1.43	-0.54	-0.62	-0.37	1.78	-1.04	1.87	1.97
mdtA	multidrug efflux system subunit A	5.50	2.58	2.68	4.07	2.29	2.52	1.11	1.09
mdtB	multidrug efflux system subunit B	5.98	2.64	1.32	4.28	1.51	0.79	0.50	0.96
mdtC	multidrug efflux system subunit C	5.09	1.38	0.48	3.15	0.72	0.00	0.30	0.86
mdtE	anaerobic multidrug efflux transporter ArcA-regulated	-1.39	0.47	-0.16	-2.84	-0.16	-0.67	-0.57	-0.05

Gene	**COG Annotation**	**Log$_2$ Fold Change of FPKM ***							
		Sertraline 1 mg/L-chloramphenicol	**Sertraline 1 mg/L-tetracycline**	**Sertraline 1 mg/L-ciprofloxacin**	**Sertraline 1 mg/L-amoxicillin**	**Sertraline 50 mg/L-chloramphenicol**	**Sertraline 50 mg/L-tetracycline**	**Sertraline 50 mg/L-ciprofloxacin**	**Sertraline 50 mg/L-amoxicillin**
mdtF	anaerobic multidrug efflux transporter ArcA-regulated	-1.48	0.33	-0.17	-2.20	-0.01	-0.29	-0.28	0.54
mdtM	multidrug efflux system protein	-4.23	-4.14	-1.05	-3.78	0.27	-1.87	-1.95	-1.59
mlaA	ABC transporter maintaining OM lipid asymmetry OM lipoprotein component	0.82	0.67	0.24	0.41	0.27	-0.23	0.18	0.39
mlaB	ABC transporter maintaining OM lipid asymmetry cytoplasmic STAS component	2.60	1.36	1.33	2.47	1.50	0.05	1.14	0.89
mlaC	ABC transporter maintaining OM lipid asymmetry periplasmic binding protein	1.18	1.09	0.46	1.07	0.73	0.20	0.69	0.67
mlaF	ABC transporter maintaining OM lipid asymmetry ATP-binding protein	0.82	0.71	0.41	0.98	0.69	0.41	0.71	0.91
mntP	putative Mn(2+) efflux pump mntR-regulated	-1.19	-1.68	-3.54	-1.25	-1.35	-2.04	-1.74	-1.60
nikB	nickel ABC transporter permease	1.81	1.88	1.08	1.53	1.74	0.97	1.62	1.26
oppA	oligopeptide ABC transporter periplasmic binding protein	0.65	0.26	0.40	0.32	0.11	0.51	0.73	0.23
oppB	oligopeptide ABC transporter permease	0.00	-1.86	-0.48	-0.16	-1.58	-1.41	-1.21	-0.96
oppC	oligopeptide ABC transporter permease	0.28	-0.35	-1.24	0.18	-1.31	-0.80	-0.35	-0.46
oppD	oligopeptide ABC transporter ATPase	1.11	0.32	-0.03	1.04	0.28	0.81	0.67	0.64

Gene	COG Annotation	Log$_2$ Fold Change of FPKM [*]							
		Sertraline 1 mg/L-chloramphenicol	**Sertraline 1 mg/L-tetracycline**	**Sertraline 1 mg/L-ciprofloxacin**	**Sertraline 1 mg/L-amoxicillin**	**Sertraline 50 mg/L-chloramphenicol**	**Sertraline 50 mg/L-tetracycline**	**Sertraline 50 mg/L-ciprofloxacin**	**Sertraline 50 mg/L-amoxicillin**
phnC	phosphonate ABC transporter ATPase	4.99	5.63	1.35	7.01	1.92	1.51	0.84	1.77
phnD	phosphonate ABC transporter periplasmic binding protein	4.40	3.59	1.47	5.83	1.08	1.18	0.55	0.12
pstA	phosphate ABC transporter permease	5.66	4.17	3.14	5.50	2.12	1.65	2.51	2.46
pstB	phosphate ABC transporter ATPase	5.31	3.66	2.35	5.26	1.45	1.39	2.15	1.69
pstC	phosphate ABC transporter permease	5.31	3.98	3.34	5.18	2.65	1.67	2.16	2.07
pstS	phosphate ABC transporter periplasmic binding protein	7.34	6.70	6.13	7.32	4.91	5.00	4.61	4.39
rcnB	periplasmic modulator of Ni and Co efflux	1.24	1.42	0.79	1.23	0.61	0.54	0.39	0.22
ssuB	aliphatic sulfonate ABC transporter ATPase	0.99	0.74	-0.36	0.36	-0.20	0.69	1.25	0.56
tatE	TatABCE protein translocation system subunit	0.96	1.46	0.36	-0.41	-0.78	0.74	0.63	0.06
tolB	periplasmic protein	0.77	-0.03	0.29	0.67	0.40	-0.01	-0.18	-0.42
tolC	transport channel	0.69	1.48	1.15	0.20	1.31	0.52	0.60	0.55
tolR	membrane spanning protein in TolA-TolQ-TolR complex	1.70	0.06	0.25	1.81	0.64	-0.23	0.61	1.25
ybbA	putative ABC transporter ATPase	3.72	2.59	1.55	2.06	0.69	1.34	0.88	0.10
ybbP	putative ABC transporter permease	2.26	1.01	0.50	0.79	0.34	0.16	-0.30	0.20
ybhS	putative ABC transporter permease	0.44	0.24	-0.72	0.36	-0.59	-0.66	-0.22	0.22
yciK	putative EmrKY-TolC system oxoacyl-(acyl carrier protein) reductase	1.97	1.71	1.37	1.94	0.92	1.26	0.82	0.51

Gene	**COG Annotation**	**Log$_2$ Fold Change of FPKM** *							
		Sertraline 1 mg/L-chloramphenicol	**Sertraline 1 mg/L-tetracycline**	**Sertraline 1 mg/L-ciprofloxacin**	**Sertraline 1 mg/L-amoxicillin**	**Sertraline 50 mg/L-chloramphenicol**	**Sertraline 50 mg/L-tetracycline**	**Sertraline 50 mg/L-ciprofloxacin**	**Sertraline 50 mg/L-amoxicillin**
ydhI	DUF1656 family putative inner membrane efflux pump associated protein	-2.83	-4.72	-2.47	-2.33	-0.80	-1.71	-4.62	-1.62

*: Comparing with the mutant control group without any sertraline dosage

Table S9 Proteins related to efflux pump in antidepressant sertraline- induced (60 days) mutants, after the exposure of 50 mg/L sertraline

Protein	**Description**	**Log$_2$ Fold Change of FPKM** [*]							
		Sertraline 1 mg/L-chloramphenicol	**Sertraline 1 mg/L-tetracycline**	**Sertraline 1 mg/L-ciprofloxacin**	**Sertraline 1 mg/L-amoxicillin**	**Sertraline 50 mg/L-chloramphenicol**	**Sertraline 50 mg/L-tetracycline**	**Sertraline 50 mg/L-ciprofloxacin**	**Sertraline 50 mg/L-amoxicillin**
AcrA	Multidrug efflux pump subunit	-1.61	-0.72	-2.74	0.51	0.22	0.30	-0.42	-0.61
AcrB	Multidrug efflux pump subunit	-1.50	-0.56	-2.66	0.55	0.46	0.45	-0.35	0.09
BamD	Outer membrane protein assembly factor	0.28	0.50	0.75	0.53	0.36	0.34	0.05	-0.07
FtsN	Cell division protein	-0.23	0.13	-0.97	-0.21	0.00	0.22	-0.39	-0.73
MdtA	Multidrug resistance protein	1.51	-0.26	1.66	0.54	-2.12	-6.64	0.11	-6.64
PstB	Phosphate import ATP-binding protein	2.02	1.44	1.60	1.11	0.94	1.67	1.48	1.13
PstS	Phosphate-binding protein	3.05	2.38	2.64	0.42	0.62	0.35	2.05	-0.05
RcnB	Nickel/cobalt homeostasis protein	0.87	1.16	0.69	0.15	0.09	0.70	0.72	-0.37
TolA	Tol-Pal system protein	0.14	0.20	0.21	0.05	-0.01	0.23	0.35	-0.38
TolB	Tol-Pal system protein	0.08	0.01	0.63	0.03	-0.42	-0.41	0.45	-0.76
TolC	Outer membrane protein	0.19	1.09	-1.48	1.17	0.35	0.62	-0.17	-0.70
TolQ	Tol-Pal system protein	0.53	0.41	0.25	0.41	0.95	0.39	0.24	1.70
TolR	Tol-Pal system protein	-0.03	0.05	0.48	0.63	0.42	0.03	0.32	0.19
YciK	Uncharacterized oxidoreductase	0.47	0.95	0.17	0.89	0.09	0.57	0.32	-0.56

[*]: Comparing with the mutant control group without any sertraline dosage

Table S10 Genes related to membrane in *E. coli* MG1655 after exposure of antidepressants

Gene	**COG Annotation**	**Log$_2$ Fold Change of FPKM** *					
		Sertraline 1 mg/L	**Sertraline 50 mg/L**	**Duloxetine 50 mg/L**	**Bupropion 50 mg/L**	**Escitalopram 50 mg/L**	**Agomelatine 50 mg/L**
alx	putative membrane-bound redox modulator	-1.28	1.94	-1.08	-1.17	-1.73	-1.37
asmA	suppressor of OmpF assembly mutants putative outer membrane protein assembly factor inner membrane-anchored periplasmic protein	-0.24	-1.12	-0.50	-0.03	0.07	-0.43
exbB	membrane spanning protein in TonB-ExbB-ExbD complex	0.03	-2.39	-1.02	-0.39	-1.26	-0.47
exbD	membrane spanning protein in TonB-ExbB-ExbD complex	0.03	-1.99	-1.18	-0.38	-0.75	-0.33
fecA	TonB-dependent outer membrane ferric citrate transporter and signal transducer ferric citrate extracelluar receptor FecR-interacting protein	0.41	-1.91	-0.47	-0.22	-0.68	0.02
fecR	anti-sigma transmembrane signal transducer for ferric citrate transport periplasmic FecA-bound ferric citrate sensor and cytoplasmic FecI ECF sigma factor activator	0.29	-3.44	-1.41	-0.31	-1.25	0.21
ftsL	membrane bound cell division leucine zipper septum protein	0.67	1.08	0.51	0.45	0.79	0.20
ftsQ	divisome assembly protein membrane anchored protein involved in growth of wall at septum	0.87	1.34	1.10	0.62	0.61	0.64
lamB	maltose outer membrane porin (maltoporin)	0.04	-1.13	0.20	-0.25	-0.50	-0.45
ompA	outer membrane protein A	0.52	0.71	0.94	0.34	-0.74	0.97
ompC	outer membrane porin protein C	0.04	-0.99	0.13	0.16	-0.15	0.14
ompF	outer membrane porin 1a	-1.73	-3.32	-3.20	-2.12	-2.70	-2.46
ompG	outer membrane porin G	-0.06	-0.41	-1.66	-2.11	-0.99	-2.36
ompN	outer membrane pore protein N non-specific	-1.16	2.29	0.47	-0.35	-0.10	-0.52
ompR	response regulator in two-component regulatory system with EnvZ	-0.10	2.47	0.44	-0.04	-0.38	0.64
ompT	DLP12 prophage outer membrane protease VII outer membrane protein 3b	-0.37	-3.22	-1.40	-1.17	-2.24	-1.01
ompW	outer membrane protein W	0.63	0.03	0.33	1.20	2.02	1.08
ompX	outer membrane protein X	0.29	2.53	1.27	0.69	-0.27	1.05
phoE	outer membrane phosphoporin protein E	-0.47	2.09	-0.93	-1.91	-1.28	-0.86

Gene	**COG Annotation**	**Log$_2$ Fold Change of FPKM** [*]					
		Sertraline 1 mg/L	**Sertraline 50 mg/L**	**Duloxetine 50 mg/L**	**Bupropion 50 mg/L**	**Escitalopram 50 mg/L**	**Agomelatine 50 mg/L**
tonB	membrane spanning protein in TonB-ExbB-ExbD transport complex	-0.44	-1.27	-0.68	-0.47	-0.98	-0.61
yddB	putative TonB-dependent outer membrane receptor	0.13	-1.20	0.28	0.13	-0.75	0.65

[*]: Comparing with the non-antidepressant control group

Table S11 Proteins related to membrane in *E. coli* MG1655 after exposure of antidepressants

Protein	Description	Log$_2$ Fold Change of Protein Abundance[*]					
		Sertraline 1 mg/L	**Sertraline 50 mg/L**	**Duloxetine 50 mg/L**	**Bupropion 50 mg/L**	**Escitalopram 50 mg/L**	**Agomelatine 50 mg/L**
AsmA	Membrane porin	-0.04	-0.29	-0.16	-0.05	0.24	0.08
FtsA	Cell division protein	-0.12	0.44	0.12	-0.30	0.57	-0.30
FtsE	Cell division ATP-binding protein	-0.10	0.29	0.05	-0.10	0.09	0.05
FtsH	ATP-dependent protein	-0.01	-0.09	0.05	0.05	0.09	0.15
FtsN	Cell division protein	0.43	0.28	0.30	0.46	-0.13	0.21
FtsZ	Cell division protein	-0.05	0.44	0.20	-0.02	0.17	0.05
OmpA	Outer membrane protein A	0.33	0.21	0.32	0.64	0.01	0.18
OmpC	Outer membrane porin C	0.31	0.05	-0.03	0.46	-0.13	-0.02
OmpF	Outer membrane porin F	0.16	0.15	0.04	0.18	-0.35	-0.09
OmpR	Transcriptional regulatory protein	-0.22	0.98	0.60	-0.27	0.12	-0.02
OmpT	Protease	0.02	-1.80	-1.37	0.17	-0.08	-0.26
OmpW	Outer membrane protein W	0.23	0.05	0.19	0.25	0.02	-0.16
OmpX	Outer membrane protein X	0.40	0.89	1.00	0.63	-0.04	-0.03
PhoA	Alkaline phosphatase	0.18	0.12	-0.95	0.03	0.20	0.42
PhoP	Transcriptional regulatory protein	-0.06	-0.12	-0.01	-0.08	0.20	0.20
PhoQ	Sensor protein	-0.26	-1.07	-0.40	0.09	0.23	0.42
PhoU	Phosphate-specific transport system accessory protein	-0.03	1.92	0.35	-0.13	0.31	0.29

[*]: Comparing with the non-antidepressant control group

Table S12 Genes related to membrane in antidepressant sertraline- induced (60 days) mutants, after the exposure of 50 mg/L sertraline

Gene	**COG Annotation**	**Log$_2$ Fold Change of FPKM***							
		Sertraline 1 mg/L-chloramph-enicol	**Sertraline 1 mg/L-tetracycline**	**Sertraline 1 mg/L-ciprofloxacin**	**Sertraline 1 mg/L-amoxicillin**	**Sertraline 50 mg/L-chloramph-enicol**	**Sertraline 50 mg/L-tetracycline**	**Sertraline 50 mg/L-ciprofloxacin**	**Sertraline 50 mg/L-amoxicillin**
alx	putative membrane-bound redox modulator	2.73	0.11	0.03	0.95	0.05	-0.11	-1.35	-0.76
asmA	suppressor of OmpF assembly mutants putative outer membrane protein assembly factor inner membrane-anchored periplasmic protein	-0.50	-0.19	-0.35	-0.53	-0.72	-0.12	-0.12	0.00
exbB	membrane spanning protein in TonB-ExbB-ExbD complex	-2.09	-1.60	-1.57	-2.00	-1.31	-1.48	-0.72	-1.35
exbD	membrane spanning protein in TonB-ExbB-ExbD complex	-2.00	-1.86	-1.41	-1.91	-1.59	-1.72	-0.89	-1.19
fecA	TonB-dependent outer membrane ferric citrate transporter and signal transducer ferric citrate extracelluar receptor FecR-interacting protein	-0.48	0.01	-0.39	-0.38	-0.90	-0.27	-0.32	-0.27
fecR	anti-sigma transmembrane signal transducer for ferric citrate transport periplasmic FecA-bound ferric citrate sensor and cytoplasmic FecI ECF sigma factor activator	-1.80	-1.13	-1.81	-0.82	-1.15	-2.86	0.09	-0.90
ftsL	membrane bound cell division leucine zipper septum protein	0.76	0.73	-0.09	1.45	0.33	0.22	0.44	0.20
ftsQ	divisome assembly protein membrane anchored protein involved in growth of wall at septum	0.78	0.65	0.42	0.82	-0.14	0.62	0.61	0.34
lamB	maltose outer membrane porin (maltoporin)	-1.42	0.23	1.05	-0.78	1.19	0.07	3.31	0.13
ompA	outer membrane protein A	0.55	0.98	1.43	1.33	1.37	0.97	1.80	0.89
ompC	outer membrane porin protein C	-0.24	0.78	1.19	-0.92	0.98	0.85	1.34	0.21
ompF	outer membrane porin 1a	-2.37	-2.06	-1.73	-2.08	-1.76	-1.37	-2.09	-1.92
ompG	outer membrane porin G	-1.92	-1.31	-0.33	-0.26	-4.67	-1.78	6.66	-0.81

Gene	COG Annotation	Log$_2$ Fold Change of FPKM [*]							
		Sertraline 1 mg/L-chloramphenicol	**Sertraline 1 mg/L-tetracycline**	**Sertraline 1 mg/L-ciprofloxacin**	**Sertraline 1 mg/L-amoxicillin**	**Sertraline 50 mg/L-chloramphenicol**	**Sertraline 50 mg/L-tetracycline**	**Sertraline 50 mg/L-ciprofloxacin**	**Sertraline 50 mg/L-amoxicillin**
ompN	outer membrane pore protein N non-specific	0.70	2.31	0.59	1.52	1.53	0.08	2.11	1.52
ompR	response regulator in two-component regulatory system with EnvZ	1.01	0.76	0.35	0.51	0.93	0.23	1.01	0.66
ompT	DLP12 prophage outer membrane protease VII outer membrane protein 3b	-0.38	0.04	0.07	-1.88	-0.30	1.01	1.14	0.93
ompW	outer membrane protein W	0.93	1.24	1.73	0.96	1.28	1.61	2.91	0.89
ompX	outer membrane protein X	1.85	1.79	1.34	2.16	1.10	0.63	0.46	0.67
phoE	outer membrane phosphoporin protein E	0.78	-0.30	-1.63	1.51	-0.99	-0.85	-0.15	-1.70
tonB	membrane spanning protein in TonB-ExbB-ExbD transport complex	-0.98	-0.54	-0.42	-1.38	-0.63	-1.18	0.19	-0.31
yddB	putative TonB-dependent outer membrane receptor	-1.42	-2.18	-1.72	-1.43	-1.78	-1.72	-0.74	-1.38

[*]: Comparing with the mutant control group without any sertraline dosage

Table S13 Proteins related to membrane in antidepressant sertraline- induced (60 days) mutants, after the exposure of 50 mg/L sertraline

Protein	**Description**	**Log$_2$ Fold Change of FPKM** *							
		Sertraline 1 mg/L-chloramphenicol	**Sertraline 1 mg/L-tetracycline**	**Sertraline 1 mg/L-ciprofloxacin**	**Sertraline 1 mg/L-amoxicillin**	**Sertraline 50 mg/L-chloramphenicol**	**Sertraline 50 mg/L-tetracycline**	**Sertraline 50 mg/L-ciprofloxacin**	**Sertraline 50 mg/L-amoxicillin**
AsmA	Membrane porin	-0.09	0.00	0.14	0.07	-0.19	-0.05	-0.19	-0.06
FtsA	Cell division protein	1.61	0.45	1.65	2.44	-2.08	-1.65	0.93	1.27
FtsE	Cell division ATP-binding protein	0.22	0.60	0.44	0.33	0.59	0.77	0.06	0.32
FtsH	ATP-dependent protein	0.31	0.57	0.32	0.24	0.54	0.60	-0.08	0.22
FtsN	Cell division protein	-0.23	0.13	-0.21	-0.97	0.00	0.22	-0.73	-0.39
FtsZ	Cell division protein	0.29	0.27	0.41	0.79	-0.03	-0.02	-0.34	0.35
OmpA	Outer membrane protein A	0.31	0.20	0.58	1.07	0.23	0.20	0.24	0.45
OmpC	Outer membrane porin C	-0.09	-0.50	-0.02	-1.31	0.01	0.07	-1.07	-0.80
OmpF	Outer membrane porin F	1.94	0.05	-0.34	2.65	-0.44	-1.25	-2.35	0.82
OmpR	Transcriptional regulatory protein	-0.86	-0.22	-0.66	-0.99	-0.22	-0.94	-1.12	-0.72
OmpT	Protease	0.67	0.26	0.47	1.65	-1.35	-0.23	0.31	0.08
OmpW	Outer membrane protein W	-0.29	-0.80	-0.15	0.03	-0.26	0.04	0.21	0.02
OmpX	Outer membrane protein X	0.36	0.95	0.91	1.08	-0.22	-0.13	0.39	-0.54
PhoA	Alkaline phosphatase	1.58	1.06	-0.42	0.48	0.02	0.23	0.64	0.21
PhoP	Transcriptional regulatory protein	-0.38	-0.62	-0.47	0.03	-0.36	-0.81	-1.84	0.06
PhoU	Phosphate-specific transport system accessory protein	1.89	0.94	0.43	1.84	0.01	0.21	-0.47	0.77

*: Comparing with the mutant control group without any sertraline dosage

Table S14 The nonsynonymous single nucleotide polymorphisms (SNPs) caused by antidepressant exposed whole bacterial population

Gene Name	Position	Gene No	Gene + / -	Summary	Wild-type *E. coli*	Sertraline 50 mg/L (15-day)	Sertraline 50 mg/L (30-day)	Sertraline 50 mg/L (60-day)	Duloxetine 50 mg/L (15-day)	Duloxetine 50 mg/L (30-day)	Duloxetine 50 mg/L (60-day)	Buprопion 100 mg/L (30-day)	Escitalopram 100 mg/L (30-day)	Agomelatine 100 mg/L (30-day)
pcnB	159101	140	-	poly(A) polymerase	AACGCCGTTTT	AACGCCATTTT		AACGCCATTTT	AACGCCATTTT				AACGCCATTTT	AACGCCATTTT
acrR	485786 486067	469	+	transcriptional repressor (Note: acrAB operon repressor)	TTGCGCTTCTT CTTCTGTCACC	TTGCGCATCTT CTTCTGTTACC	TTGCGCATCTT CTTCTGTTACC	TTGCGCATCTT CTTCTGTTACC	TTGCGCATCTT CTTCTGTTACC	TTGCGCATCTT CTTCTGTTACC	TTGCGCATCTT CTTCTGTTACC			
rzpD	578200 & 578210	564	+	Overexpression causes abnormal biofilm architecture	TAACGCAATCG CCTACAAAGTC CAGCGCGAC	TAACGCAATCA CCTACAAAGCC CAGCGCGAC	TAACGCAATCA CCTACAAAGCC CAGCGCGAC	TAACGCAATCA CCTACAAAGCC CAGCGCGAC	TAACGCAATCA CCTACAAAGCC CAGCGCGAC	TAACGCAATCA CCTACAAAGCC CAGCGCGAC	TAACGCAATCA CCTACAAAGCC CAGCGCGAC	TAACGCAATCA CCTACAAAGCC CAGCGCGAC	TAACGCAATCA CCTACAAAGCC CAGCGCGAC	TAACGCAATCA CCTACAAAGCC CAGCGCGAC
tfaD	581914	572	+	NA (Note: pseudogene DLP12 prophage tail fiber assembly protein family Phage or Prophage Related)	AAAACAGCCTG	AAAAAAGCCTG	AAAAAAGCCTG	AAAAAAGCCTG	AAAAAAGCCTG	AAAAAAGCCTG	AAAAAAGCCTG	AAAAAAGCCTG	AAAAAAGCCTG	AAAAAAGCCTG
ompT	585201 & 585204 & 585208 & 585213 & 585216 & 585228 585350 & 585351 & 585378 & 585384	576	-	DLP12 prophage outer membrane protease VII outer membrane protein (Note: outer membrane protein protease VII)	AACCCAAGCAA CTCCTCGGTCG GAAACTATA GGCTCTCAACA GGTCGGTCGTC GGGGCTATCTA TAG	ATCCGAAGGAA CTGCTGGGTCG GAAACTTTA GGCTCTCAACA GGTCGGTCGTC GGGGCTATCTA TAG	ATCCGAAGGAA CTGCTGGGTCG GAAACTTTA GGCTCTCAACA GGTCGGTCGTC GGGGCTATCTA TAG	ATCCGAAGGAA CTGCTGGGTCG GAAACTTTA GGCTCTCAACA GGTCGGTCGTC GGGGCTATCTA TAG	ATCCGAAGGAA CTGCTGGGTCG GAAACTTTA GGCTCTCAACA GGTCGGTCGTC GGGGCTATCTA TAG	ATCCGAAGGAA CTGCTGGGTCG GAAACTTTA GGCTCTCAACA GGTCGGTCGTC GGGGCTATCTA TAG	ATCCGAAGGAA CTGCTGGGTCG GAAACTTTA GGCTCTCAACA GGTCGGTCGTC GGGGCTATCTA TAG	ATCCGAAGGAA CTGCTGGGTCG GAAACTTTA	ATCCGAAGGAA CTGCTGGGTCG GAAACTTTA	ATCCGAAGGAA CTGCTGGGTCG GAAACTTTA
elfC	999430	954	-	putative fimbrial usher protein	GAACAATATCG					GAACAGTATCG				
helD	1026442	976	+	DNA helicase IV	CAGTGCCCATA	CATTGCCCATA	CATTGCCCATA	CATTGCCCATA	CATTGCCCATA	CATTGCCCATA	CATTGCCCATA	CATTGCCCATA		CATTGCCCATA
stfR	1431795 1432070 & 1432079	1403	+	Rac prophage putative tail fiber protein; putative membrane protein	GAACGGTATCT CACATACACAC AGTGT	GAACGCTATCT CACATGCACAC AGTCT	GAACGCTATCT CACATGCACAC AGTCT	GAACGCTATCT CACATGCACAC AGTCT	CACATGCACAC AGTCT	GAACGCTATCT CACATGCACAC AGTCT	GAACGCTATCT CACATGCACAC AGTCT	GAACGCTATCT CACATGCACAC AGTCT	CACATGCACAC AGTCT	CACATGCACAC AGTCT
marR	1619136 1619249 1619331 & 1619336	1564	+	transcriptional repressor of multiple antibiotic resistance (Note: multiple antibiotic resistance protein repressor of mar operon)	CAGATCGCTGG GCACCTTAAAC ATACGGGTCAG	CAGATCTCTGG	ACACGGTTCAG	CAGATCTCTGG ACACGGTTCAG	GCACTTTAAAC ACACGGTTCAG	ACACGGTTCAG	GCACTTTAAAC ACACGGTTCAG			
tfaQ	1634404	1582	-	putative tail fiber assembly protein	AAGAAATCTCG	AAGAGATCTCG							AAGAGATCTCG	
stfQ	1635340	1583	-	Qin prophage putative side tail fibre assembly protein	GCATGACCTAC	GCATGTCCTAC	GCATGTCCTAC	GCATGTCCTAC	GCATGTCCTAC	GCATGTCCTAC	GCATGTCCTAC	GCATGTCCTAC	GCATGTCCTAC	GCATGTCCTAC
nohA	1635974	1584	+	putative prophage DNA-packaging protein	GACGGGATCCC	GACGTGATCCC	GACGTGATCCC		GACGTGATCCC	GACGTGATCCC		GACGTGATCCC	GACGTGATCCC	GACGTGATCCC
sufB	1763716	1724	-	Fe-S cluster scaffold complex subunit SufB	GTAATTGTGAC	GTAATTCTGAC								
rpoA	3440378	3357	+	RNA polymerase subunit alpha	GGCGATTCGTC		GGCTATTCGTC							
aroK	3518961	3452	+	shikimate kinase 1	GATTCCGATCA	GATTCCAATCA								

Gene Name	Position	Gene No	Gene + / -	Summary	Wild-type *E. coli*	Sertraline 50 mg/L (15-day)	Sertraline 50 mg/L (30-day)	Sertraline 50 mg/L (60-day)	Duloxetine 50 mg/L (15-day)	Duloxetine 50 mg/L (30-day)	Duloxetine 50 mg/L (60-day)	Bupropion 100 mg/L (30-day)	Escitalopram 100 mg/L (30-day)	Agomelatine 100 mg/L (30-day)
yhjC	3672693 & 3672694	3587	+	LysR family putative transcriptional regulator (Note: putative transcriptional regulator LYSR-type)	AAAT**T**			AAAT**G**			AAAT**G**		AAAT**G**	AAAT**G**
yiaL	3743946 & 3743948	3648	+	DUF386 family protein (Note: putative lipase)	**T**A**T**CGATATTC			**G**A**G**CGATATTC					**G**A**G**CGATATTC	
lamB	4248598	4119	+	maltose outer membrane porin (maltoporin) (Note: phage lambda receptor protein maltose high-affinity receptor)	ACCCGGGC**G**GC		ACCCGGGC**A**GC					ACCCGGGC**A**GC		
ssb	4274329 & 4274336 & 4274350	4143	+	single-stranded DNA-binding protein (Note: ssDNA-binding protein)	GGCG**A**GCGAAT**A**TCTGCGTAAAGGT**T**CTCAG	GGCG**G**GCGAAT**G**TCTGCGTAAAGGT**G**CTCAG		GGCG**G**GCGAAT**G**TCTGCGTAAAGGT**G**CTCAG	GGCG**G**GCGAAT**G**TCTGCGTAAAGGT**G**CTCAG	GGCG**G**GCGAAT**G**TCTGCGTAAAGGT**G**CTCAG		GGCG**G**GCGAAT**G**TCTGCGTAAAGGT**G**CTCAG	GGCG**G**GCGAAT**G**TCTGCGTAAAGGT**G**CTCAG	GGCG**G**GCGAAT**G**TCTGCGTAAAGGT**G**CTCAG
rob	4635103	4490	-	right oriC-binding transcriptional activator AraC family (Note: right origin-binding protein)	TACC**G**CCTTTA					TACC**T**CCTTTA				

Table S15 The nonsynonymous single nucleotide polymorphisms (SNPs) caused by antidepressant induced mutants

Gene Name	Position	Gene No.	Gene +/-	Summary	Wild-type *E. coli*	Sertraline 50 mg/L (1-day)		Sertraline 1 mg/L (60-day)		Sertraline 50 mg/L(30-day)	Sertraline 50 mg/L (60-day)				Duloxetine 50 mg/L (30-day)	Bupropion 100 mg/L (30-day)	Escitalopram 50 mg/L (30-day)
						Chloramphenicol	Tetracycline	Chloramphenicol	Tetracycline	Chloramphenicol	Chloramphenicol	Tetracycline	Ciprofloxacin	Amoxicillin	Chloramphenicol	Chloramphenicol	Chloramphenicol
folK	157371	139	-	2-amino-4-hydroxy-6-hydroxymethyldihydropteridine diphosphokinase	AAGAAT**C**GTGG					AAGAAT**G**GTGG					AAGAAT**G**GTGG		
pcnB	159101	140	-	poly(A) polymerase	AACGCC**G**TTTT		AACGCC**A**TTTT			AACGCC**A**TTTT	AACGCC**A**TTTT					AACGCC**A**TTTT	
queC	464899	449	-	7-cyano-7-deazaguanine (preQ0) synthase queuosine biosynthesis	GGCAGCCAA**A**T	GGCAGCCAA**G**T											
acrR	486133 & 486134	469	+	transcriptional repressor (Note: acrAB operon repressor)	GCT**GT**TGTGCA					GCTG**A**TGTGCA	GCTG**A**TGTGCA			GCT**AA**TGTGCA			
	486227 & 486233				TG**C**GGATT**T**A							TG**T**GGATT**C**AA					
peaD	566565	545	+	NA (Note: pseudogene DLP12 prophage replication protein family Phage or Prophage Related)	GTGAG**A**CGATA			GTGAG**G**CGATA	GTGAG**G**CGATA		GTGAG**G**CGATA	GTGAG**G**CGATA	GTGAG**G**CGATA	GTGAG**G**CGATA	GTGAG**G**CGATA	GTGAG**G**CGATA	
renD	566728 & 566742 & 566756	546	-	Putative membrane protein	TA**C**CGCGGCAACG**T**CC**T**GTGCACAGAAGCT**C**TC										TA**G**CGCGGCAACG**T**CC**A**GTGCACAGAAGCT**G**TC		
rzpD	578200 & 578210	564	+	Overexpression causes abnormal biofilm architecture	TAACGCAATC**G**CCTACAAAG**T**CCAGCGCGAC	TAACGCAATC**A**CCTACAAAG**C**CCAGCGCGAC	TAACGCAATCGCCTACAAAG**C**CCAGCGCGAC	TAACGCAATC**A**CCTACAAAG**C**CCAGCGCGAC	TAACGCAATC**A**CCTACAAAG**C**CCAGCGCGAC	TAACGCAATC**A**CCTACAAAG**C**CCAGCGCGAC	TAACGCAATC**A**CCTACAAAG**C**CCAGCGCGAC	TAACGCAATC**A**CCTACAAAG**C**CCAGCGCGAC	TAACGCAATC**A**CCTACAAAG**C**CCAGCGCGAC	TAACGCAATC**A**CCTACAAAG**C**CCAGCGCGAC	TAACGCAATC**A**CCTACAAAG**C**CCAGCGCGAC	TAACGCAATC**A**CCTACAAAG**C**CCAGCGCGAC	TAACGCAATC**A**CCTACAAAG**C**CCAGCGCGAC
tfaD	581914	572	+	NA (Note: pseudogene DLP12 prophage tail fiber assembly protein family Phage or Prophage Related)	AAAA**C**AGCCTG			AAAA**A**AGCCTG	AAAA**A**AGCCTG		AAAA**A**AGCCTG		AAAA**A**AGCCTG	AAAA**A**AGCCTG		AAAA**A**AGCCTG	AAAA**A**AGCCTG
ompT	585201 & 585204 & 585208 & 585213 & 585216 & 585228	576	-	DLP12 prophage outer membrane protease VII outer membrane protein (Note: outer membrane protein protease VII)	A**A**CC**C**AAG**C**AACT**C**CT**C**GGTCGGAAACT**A**TA	A**T**CC**G**AAG**G**AACT**G**CT**G**GGTCGGAAACT**T**TA		A**C**CC**A**AAG**T**AACT**A**CT**A**GGTCGGAAACT**C**TA	A**C**CC**A**AAG**T**AACT**A**CT**A**GGTCGGAAACT**C**TA	A**T**CC**G**AAG**G**AACT**G**CT**G**GGTCGGAAACT**T**TA	A**C**CC**A**AAG**T**AACT**A**CT**A**GGTCGGAAACT**C**TA	A**C**CC**A**AAG**T**AACT**A**CT**A**GGTCGGAAACT**C**TA	A**C**CC**A**AAG**T**AACT**A**CT**A**GGTCGGAAACT**C**TA	A**C**CC**A**AAG**T**AACT**A**CT**A**GGTCGGAAACT**C**TA	A**C**CC**A**AAG**T**AACT**A**CT**A**GGTCGGAAACT**C**TA	A**C**CC**A**AAG**T**AACT**A**CT**A**GGTCGGAAACT**C**TA	A**C**CC**A**AAG**T**AACT**A**CT**A**GGTCGGAAACT**C**TA
	585259 & 585260				ACTC**AA**CACAT	ACTC**TT**CACAT											
	585302				CC**A**ATGACCTT	CC**T**ATGACCTT											

Gene Name	Position	Gene No.	Gene +/-	Summary	Wild-type *E. coli*	Sertraline 50 mg/L (1-day)		Sertraline 1 mg/L (60-day)		Sertraline 50 mg/L(30-day)	Sertraline 50 mg/L (60-day)				Duloxetine 50 mg/L (30-day)	Bupropion 100 mg/L (30-day)	Escitalopram 50 mg/L (30-day)
						Chloramphenicol	Tetracycline	Chloramphenicol	Tetracycline	Chloramphenicol	Chloramphenicol	Tetracycline	Ciprofloxacin	Amoxicillin	Chloramphenicol	Chloramphenicol	Chloramphenicol
	585350 & 585351 & 585378 & 585384				GGCTCTCAACAGGTCGGTCGTCGGGGCTATCTATAG	CCCTCTCAACAGGTCGGTCGTCGGGGCTTTCTATTG										GGCTCTCAACAGGTCGGTCGTCGGGGCTTTCTATTG	
deoR	882439	853	-	deoxyribose-5-phosphate-inducible deoxyribose operon transcriptional repressor repressor of nupG and tsx (Note: transcriptional repressor for deo operon tsx nupG)	TGTCAGTTTTT									TGTCCGTTTTT			
stfP	1207789	1168	+	e14 prophage uncharacterized protein	AAACCTTGGTT		AAACGTTGGTT			AAACGTTGGTT				AAACGTTGGTT			
lomR	1428925	1401	+	NA (Note: pseudogene Rac prophage lom homolog Phage or Prophage Related~interrupted by IS5 and N-ter deletion)	AAGGCCCCGGC			AAGGCTCCGGC				AAGGCTCCGGC					
stfR	1430333	1403	+	Rac prophage putative tail fiber protein; putative membrane protein	GCAGCTCAGAG	GCATCTCAGAG	GCATCTCAGAG	GCATCTCAGAG	GCATCTCAGAG	GCATCTCAGAG	GCATCTCAGAG	GCATCTCAGAG	GCATCTCAGAG	GCATCTCAGAG	GCATCTCAGAG	GCATCTCAGAG	GCATCTCAGAG
	1431795				AGATACCGTTC	AGATATCGTTC	AGATATCGTTC	AGATATCGTTC	AGATATCGTTC		AGATATCGTTC	AGATATCGTTC	AGATATCGTTC				
	1432070 & 1432079				CACATACACACAGTGT			CACATGCACACAGTCT									
marR	1619136	1564	+	transcriptional repressor of multiple antibiotic resistance (Note: multiple antibiotic resistance protein repressor of mar operon)	CCAGCGATCTG				CCAGCGCTCTG								
	1619468				TAGTTGGCC			TAGTTGGCT							TAGTTGGCT		
	1619510				CGGACGAAGTG	CGGACAAAGTG											
stfQ	1635340	1583	-	Qin prophage putative side tail fibre assembly protein	GCATGACCTAC	GCATGCCCTAC	GCATGCCCTAC	GCATGCCCTAC	GCATGCCCTAC	GCATGCCCTAC	GCATGCCCTAC	GCATGCCCTAC	GCATGCCCTAC	GCATGCCCTAC	GCATGCCCTAC	GCATGCCCTAC	GCATGCCCTAC
	1635451				GTCCCTAGTGC								GTCCCTGGTGC				
nohA	1636225	1584	-	putative prophage DNA-packaging protein NohA	TATAAGATGGT					TATAATATGGT					TATAATATGGT	TATAATATGGT	TATAATATGGT
torZ	1956966 & 1956967	1921	-	trimethylamine N-oxide reductase system III catalytic subunit	TCGCCGTTATG	TCGCCGCCATG											
insF1	2171384	2145	+	IS3 transposase B	AAACAAGAACC	AAACCAGAACC			AAACCAGAACC								

Gene Name	Position	Gene No.	Gene +/-	Summary	Wild-type *E. coli*	Sertraline 50 mg/L (1-day)		Sertraline 1 mg/L (60-day)		Sertraline 50 mg/L(30-day)	Sertraline 50 mg/L (60-day)				Duloxetine 50 mg/L (30-day)	Bupropion 100 mg/L (30-day)	Escitalopram 50 mg/L (30-day)
						Chloramphenicol	Tetracycline	Chloramphenicol	Tetracycline	Chloramphenicol	Chloramphenicol	Tetracycline	Ciprofloxacin	Amoxicillin	Chloramphenicol	Chloramphenicol	Chloramphenicol
yfbN	2388374	2330	-	uncharacterized protein	GACC**T**ATGGCT	GACC**C**ATGGCT											
nuoF	2400563	2341	+	quinone oxidoreductase subunit F	TTG**A**CCATGAG												TTG**C**CCATGAG
gshA	2815806	2748	-	glutamate--cysteine ligase	AGGAAA**A**CCAA										AGGAAA**T**CCAA	AGGAAA**T**CCAA	
gcvP	3048716	2966	-	glycine decarboxylas	TGGTAT**A**CCGC										TGGTAT**T**CCGC	TGGTAT**T**CCGC	
yhhH	3623538	3544	+	putative NTF2 fold immunity protein for polymorphic toxin RhsB	AAG**G**TAAATAT						AAG**C**TAAATAT		AAG**C**TAAATAT				
gor	3647512	3561	+	glutathione oxidoreductase	TA**T**TCACGGCA	TA**G**TCACGGCA											
yhjC	3672693 & 3672694	3587	+	LysR family putative transcriptional regulator (Note: putative transcriptional regulator LYSR-type)	AAAT**T**		AAAT**G**								AAAT**G**	AAAT**G**	AAAT**G**
yhjD	3674037 & 3674038	3588	+	inner membrane putative BrbK family alternate lipid exporter	GTGGCTG**AA**AC	GTGGCTG**CC**AC											
yiaL	3743946 & 3743948	3648	+	DUF386 family protein (Note: putative lipase)	**T**A**T**CGATATTC	**G**A**G**CGATATTC											**G**A**G**CGATATTC
lamB	4248598	4119	+	maltose outer membrane porin (maltoporin) (Note: phage lambda receptor protein maltose high-affinity receptor)	ACCCGGGC**G**GC			ACCCGGGC**A**GC				ACCCGGGC**A**GC		ACCCGGGC**A**GC			
ssb	4274329 & 4274336 & 4274350	4143	+	single-stranded DNA-binding protein (Note: ssDNA-binding protein)	GGCG**A**GCGAAT**A**TCTGCGTAAAGGT**T**CTCAG	GGCG**G**GCGAAT**G**TCTGCGTAAAGGT**G**CTCAG	GGCG**G**GCGAAT**G**TCTGCGTAAAGGT**G**CTCAG	GGCG**G**GCGAAT**G**TCTGCGTAAAGGT**G**CTCAG	GGCG**G**GCGAAT**G**TCTGCGTAAAGGT**G**CTCAG	GGCG**G**GCGAAT**G**TCTGCGTAAAGGT**G**CTCAG	GGCG**G**GCGAAT**G**TCTGCGTAAAGGT**G**CTCAG	GGCG**G**GCGAAT**G**TCTGCGTAAAGGT**G**CTCAG	GGCG**G**GCGAAT**G**TCTGCGTAAAGGT**G**CTCAG	GGCG**G**GCGAAT**G**TCTGCGTAAAGGT**G**CTCAG	GGCG**G**GCGAAT**G**TCTGCGTAAAGGT**G**CTCAG	GGCG**G**GCGAAT**G**TCTGCGTAAAGGT**G**CTCAG	
cadC	4361346	4220	-	cadBA operon transcriptional activator (Note: transcriptional activator of cad operon)	ATAGCG**C**ACCT			ATAGCG**T**ACCT								ATAGCG**T**ACCT	
treB	4465070	4329	-	trehalose-specific PTS enzyme: IIB and IIC component (Note: PTS system enzyme II trehalose specific)	CCTCT**A**GAGCG								CCTCT**G**GAGCG				
rob	4634844	4490	-	right oriC-binding transcriptional activator AraC family (Note: right origin-binding protein)	TACC**G**CCTTTA						TACC**T**CCTTTA		TACC**T**CCTTTA	TACC**T**CCTTTA			

Table S16 Genes related to bacterial stress in *E. coli* MG1655 after exposure of antidepressants

Gene	**COG Annotation**	**Log$_2$ Fold Change of FPKM** *					
		Sertraline 1 mg/L	**Sertraline 50 mg/L**	**Duloxetine 50 mg/L**	**Bupropion 50 mg/L**	**Escitalopram 50 mg/L**	**Agomelatine 50 mg/L**
asr	acid shock-inducible periplasmic protein	-1.56	9.76	4.17	0.58	1.19	-0.03
ibaG	acid stress protein putative BolA family transcriptional regulator	-0.49	1.24	-1.45	-1.26	-2.13	-1.10
lexA	transcriptional repressor of SOS regulon	-0.72	-0.03	-0.22	-0.43	-0.53	-0.56
lon	DNA-binding ATP-dependent protease La	-0.02	2.30	0.53	-0.69	-1.38	-0.63
osmB	osmotically and stress inducible lipoprotein	-0.18	5.47	1.64	-0.80	-0.88	-0.46
recA	DNA recombination and repair protein ssDNA-dependent ATPase synaptase ssDNA and dsDNA binding protein ATP-dependent homologous DNA strand exchanger recombinase A LexA autocleavage cofactor	-0.46	1.89	0.39	0.04	0.09	0.05
recD	exonuclease V (RecBCD complex) alpha chain	0.19	1.17	0.57	0.28	0.86	0.17
recE	Rac prophage exonuclease VIII 5' to 3' specific dsDNA exonuclease	0.72	1.42	0.82	0.09	0.11	0.05
recF	gap repair protein	-0.29	2.18	0.15	-1.00	-0.89	-0.81
recN	recombination and repair protein	0.07	2.15	0.63	0.06	-0.26	-0.06
recX	regulatory protein for RecA	-0.56	4.28	0.66	0.07	-0.32	-0.93
rpoA	RNA polymerase alpha subunit	-0.49	3.72	0.88	-0.01	0.70	-0.12
rpoB	RNA polymerase beta subunit	-0.24	3.36	0.57	-0.15	0.50	-0.36
rpoC	RNA polymerase beta prime subunit	-0.24	3.29	0.77	-0.04	0.72	-0.21
rpoD	RNA polymerase sigma 70 (sigma D) factor	0.40	1.66	1.04	0.11	-1.18	1.03
rpoH	RNA polymerase sigma 32 (sigma H) factor	-0.04	1.91	0.71	0.01	-0.17	-0.11
rpoS	RNA polymerase sigma S (sigma 38) factor	0.20	2.71	0.57	0.17	0.81	-0.30
spy	periplasmic ATP-independent protein refolding chaperone stress-induced	-0.78	9.15	4.60	-0.32	-0.06	-0.90
srkA	Cpx stress response Thr/Ser protein kinase MazF antagonist protein	-1.45	1.47	-0.40	-1.25	-0.74	-1.74
sulA	SOS cell division inhibitor	-0.14	1.26	-0.05	0.35	0.20	-0.06
ves	cold- and stress-inducible protein	0.83	3.97	-0.67	-0.54	-0.20	0.35
yhbO	stress-resistance protein	0.15	3.87	1.15	-0.18	-0.40	-0.39
yhcN	cadmium and peroxide resistance protein stress-induced	1.11	4.93	3.43	1.85	0.19	4.01
yjbJ	stress-induced protein UPF0337 family	1.11	4.62	2.12	2.02	1.19	0.13

Gene	COG Annotation	Log$_2$ Fold Change of FPKM [*]					
		Sertraline 1 mg/L	Sertraline 50 mg/L	Duloxetine 50 mg/L	Bupropion 50 mg/L	Escitalopram 50 mg/L	Agomelatine 50 mg/L
umuC	SOS mutagenesis and repair, translesion error-prone DNA polymerase V subunit DNA polymerase activity	0.67	1.09	-0.09	0.35	-0.03	0.18
umuD	SOS mutagenesis error-prone repair processed to UmuD' forms complex with UmuC, translesion error-prone DNA polymerase V subunit RecA-activated auto-protease	0.24	1.13	0.79	0.79	0.23	0.39

[*]: Comparing with the non-antidepressant control group

Table S17 Proteins related to bacterial stress in *E. coli* MG1655 after exposure of antidepressants

Protein	**Description**	**Log$_2$ Fold Change of Protein Abundance** *					
		Sertraline 1 mg/L	**Sertraline 50 mg/L**	**Duloxetine 50 mg/L**	**Bupropion 50 mg/L**	**Escitalopram 50 mg/L**	**Agomelatine 50 mg/L**
FtsA	Cell division protein	-0.12	0.44	0.12	-0.30	0.57	-0.30
FtsN	Cell division protein	0.43	0.28	0.30	0.46	-0.13	0.21
FtsP	Cell division protein	0.04	-0.47	-0.38	-0.53	0.02	-0.27
FtsZ	Cell division protein	-0.05	0.44	0.20	-0.02	0.17	0.05
LexA	LexA repressor	0.21	0.13	-0.01	0.22	0.21	0.25
Lon	Lon protease	0.02	0.45	0.45	0.01	0.21	0.15
OsmC	Peroxiredoxin	-0.36	1.58	0.26	-0.02	0.66	0.04
Spy	Periplasmic chaperone	-0.20	-0.77	4.82	-0.03	-0.41	0.12
SrkA	Stress response kinase A	-0.14	1.60	0.62	-0.25	1.50	0.20
UspA	Universal stress protein A	0.26	0.80	0.71	0.39	0.25	-0.11
UspC	Universal stress protein C	0.04	0.43	0.25	0.13	0.02	0.33
UspD	Universal stress protein D	0.22	0.40	-0.56	-0.02	0.01	-0.28
YgiC	Putative acid--amine ligase	0.04	0.20	0.40	0.01	0.67	0.13
YgiQ	UPF0313 protein	-0.11	0.78	0.61	-0.09	0.02	0.02
YgiS	Probable deoxycholate-binding periplasmic protein	-0.02	-0.03	-0.13	-0.21	0.14	0.10
YhbT	SCP2 domain-containing protein	-0.46	1.28	1.58	-0.56	-0.32	-0.43
YhbY	RNA-binding protein	0.08	0.46	-0.13	0.58	-0.11	-0.01
YhcB	Inner membrane protein	-0.01	0.09	0.09	-0.02	-2.98	0.03
YncE	Uncharacterized protein	-0.44	-1.54	4.41	0.09	-0.06	0.12

*: Comparing with the non-antidepressant control group

Table S18 Genes related to bacterial stress in antidepressant sertraline- induced (60 days) mutants, after the exposure of 50 mg/L sertraline

Gene	**COG Annotation**	**Log$_2$ Fold Change of FPKM** *							
		Sertraline 1 mg/L-chloramphenicol	**Sertraline 1 mg/L-tetracycline**	**Sertraline 1 mg/L-ciprofloxacin**	**Sertraline 1 mg/L-amoxicillin**	**Sertraline 50 mg/L-chloramphenicol**	**Sertraline 50 mg/L-tetracycline**	**Sertraline 50 mg/L-ciprofloxacin**	**Sertraline 50 mg/L-amoxicillin**
asr	acid shock-inducible periplasmic protein	9.81	9.75	6.39	7.29	4.60	6.20	7.22	6.61
ibaG	acid stress protein putative BolA family transcriptional regulator	0.04	-0.33	-1.41	-0.68	-1.38	-1.33	-1.56	-1.47
lexA	transcriptional repressor of SOS regulon	-0.26	-0.02	-0.11	0.73	-0.83	0.24	-0.81	-0.26
lon	DNA-binding ATP-dependent protease La	3.23	-2.68	-2.75	2.53	1.32	-2.82	1.06	1.18
osmB	osmotically and stress inducible lipoprotein	5.35	3.84	2.94	5.32	2.32	2.22	2.77	1.97
recA	DNA recombination and repair protein ssDNA-dependent ATPase synaptase ssDNA and dsDNA binding protein ATP-dependent homologous DNA strand exchanger recombinase A LexA autocleavage cofactor	1.18	0.49	0.45	0.58	-0.01	0.44	-0.44	0.00
recD	exonuclease V (RecBCD complex) alpha chain	0.93	0.66	0.63	0.41	0.42	0.51	0.53	0.81
recE	Rac prophage exonuclease VIII 5' to 3' specific dsDNA exonuclease	2.85	0.79	0.46	1.32	-0.06	0.50	1.12	0.23
recF	gap repair protein	3.04	1.38	2.31	3.47	1.27	1.47	0.98	1.48
recN	recombination and repair protein	0.66	-0.47	-0.30	0.24	-1.09	-0.47	-1.34	-1.28
recX	regulatory protein for RecA	2.11	0.39	0.07	1.43	-0.05	-0.74	-0.89	-0.80
rpoA	RNA polymerase alpha subunit	2.36	1.67	1.30	1.40	1.75	0.24	0.41	1.55
rpoB	RNA polymerase beta subunit	2.25	1.75	1.18	1.20	1.31	0.81	1.00	1.32
rpoC	RNA polymerase beta prime subunit	2.01	1.81	1.55	1.28	1.72	1.00	1.43	1.73
rpoD	RNA polymerase sigma 70 (sigma D) factor	1.80	0.59	0.67	2.03	0.78	0.24	0.68	0.92
rpoH	RNA polymerase sigma 32 (sigma H) factor	1.65	1.29	2.06	1.87	1.64	1.47	0.96	0.67
rpoS	RNA polymerase sigma S (sigma 38) factor	1.37	1.13	1.17	1.10	0.85	0.58	0.90	0.81

Gene	COG Annotation	Log$_2$ Fold Change of FPKM *							
		Sertraline 1 mg/L-chloramph-enicol	Sertraline 1 mg/L-tetracycline	Sertraline 1 mg/L-ciprofloxacin	Sertraline 1 mg/L-amoxicillin	Sertraline 50 mg/L-chloramph-enicol	Sertraline 50 mg/L-tetracycline	Sertraline 50 mg/L-ciprofloxacin	Sertraline 50 mg/L-amoxicillin
spy	periplasmic ATP-independent protein refolding chaperone stress-induced	9.15	7.56	6.46	8.13	5.30	5.66	5.03	4.24
srkA	Cpx stress response Thr/Ser protein kinase MazF antagonist protein	1.80	0.42	0.52	1.26	0.47	0.26	-0.75	-0.19
sulA	SOS cell division inhibitor	0.89	-0.22	-3.33	-0.06	-1.10	-0.26	-0.62	-0.88
ves	cold- and stress-inducible protein	2.74	-0.44	0.04	1.29	-1.50	0.42	-0.35	-0.94
yhbO	stress-resistance protein	2.58	2.77	0.23	3.08	0.56	-0.71	1.14	0.10
yhcN	cadmium and peroxide resistance protein stress-induced	-0.34	0.48	1.95	-0.64	1.65	2.22	1.38	1.70
yjbJ	stress-induced protein UPF0337 family	5.06	4.84	4.22	7.08	2.64	3.30	4.33	2.89
umuC	SOS mutagenesis and repair, translesion error-prone DNA polymerase V subunit DNA polymerase activity	1.38	0.03	-0.28	0.68	-1.59	-0.08	-0.25	-0.69
umuD	SOS mutagenesis error-prone repair processed to UmuD' forms complex with UmuC, translesion error-prone DNA polymerase V subunit RecA-activated auto-protease	-0.41	-1.14	-2.14	-0.50	-2.01	-1.38	-1.26	-1.17

*: Comparing with the mutant control group without any sertraline dosage

Table S19 Proteins related to bacterial stress in antidepressant sertraline- induced (60 days) mutants, after the exposure of 50 mg/L sertraline

		Log$_2$ Fold Change of FPKM *							
Protein	**Description**	**Sertraline 1 mg/L-chloramphenicol**	**Sertraline 1 mg/L-tetracycline**	**Sertraline 1 mg/L-ciprofloxacin**	**Sertraline 1 mg/L-amoxicillin**	**Sertraline 50 mg/L-chloramphenicol**	**Sertraline 50 mg/L-tetracycline**	**Sertraline 50 mg/L-ciprofloxacin**	**Sertraline 50 mg/L-amoxicillin**
FtsA	Cell division protein	1.61	0.45	1.65	2.44	-2.08	-1.65	0.93	1.27
FtsN	Cell division protein	-0.23	0.13	-0.21	-0.97	0.00	0.22	-0.73	-0.39
FtsP	Cell division protein	-0.27	-0.32	-0.43	-0.37	-0.19	0.14	0.14	-1.72
FtsZ	Cell division protein	0.29	0.27	0.41	0.79	-0.03	-0.02	-0.34	0.35
LexA	LexA repressor	0.03	-1.23	-0.13	0.14	-1.88	-1.55	-2.94	0.04
Lon	Lon protease	1.03	-4.21	-2.99	1.09	-0.95	-3.41	-0.99	0.05
OsmC	Peroxiredoxin	1.47	0.77	-0.16	1.32	-0.87	-0.07	-1.28	1.13
Spy	Periplasmic chaperone	6.38	4.93	1.89	5.70	1.60	1.31	1.09	4.76
SrkA	Stress response kinase A	0.38	0.08	-0.12	0.53	0.02	0.58	-0.14	0.74
UspA	Universal stress protein A	0.01	0.23	-0.45	-0.11	0.13	-0.08	1.61	1.06
UspC	Universal stress protein C	1.39	1.01	1.08	1.85	0.15	2.28	1.38	1.57
UspD	Universal stress protein D	-1.16	-1.91	-0.38	-0.30	-1.53	-1.14	-0.65	-0.41
YgiC	Putative acid--amine ligase	-0.01	-0.08	-0.14	-0.73	-0.66	-0.66	-2.07	-0.09
YgiQ	UPF0313 protein	0.97	0.66	1.28	1.62	0.49	0.94	-1.85	0.75
YgiS	Probable deoxycholate-binding periplasmic protein	-0.76	-0.47	-0.91	-0.64	0.99	-6.64	3.25	1.23
YhbT	SCP2 domain-containing protein	1.29	1.93	2.23	1.88	0.06	0.22	0.13	1.26
YhbY	RNA-binding protein	0.11	0.32	-0.04	-0.29	0.89	1.04	-0.04	0.44
YhcB	Inner membrane protein	0.25	0.50	0.55	0.64	0.70	1.16	0.98	0.76
YncE	Uncharacterized protein	0.45	-0.65	-0.46	0.67	-0.12	-0.57	-0.32	-0.04

*: Comparing with the mutant control group without any sertraline dosage

Table S20 Quantified mathematical parameters and calibrated results of resistant bacteria evolution after exposure of antidepressants

		K_m	μ_W	μ_R	d_W	d_R	λ_1	λ_2	η_1	η_2
Control		4.8×10^{8}	0.158	0.106	0.03	0.035	1.0×10^{-10}	1.0×10^{-10}	1.0×10^{-9}	1.0×10^{-9}
Sertraline	0.1 mg/L	2.2×10^{8}	0.161	0.131	0.03	0.035	8.0×10^{-6}	1.0×10^{-7}	5.0×10^{-4}	4.5×10^{-5}
	1 mg/L	2.2×10^{8}	0.159	0.122	0.031	0.036	6.0×10^{-6}	2.0×10^{-7}	3.5×10^{-4}	6.0×10^{-5}
	10 mg/L	2.2×10^{8}	0.155	0.167	0.034	0.038	5.0×10^{-6}	1.0×10^{-7}	2.0×10^{-4}	3.0×10^{-5}
	50 mg/L	2.2×10^{8}	0.151	0.126	0.035	0.039	2.0×10^{-6}	5.0×10^{-7}	1.0×10^{-4}	9.0×10^{-5}
Duloxetine	0.1 mg/L	3.5×10^{8}	0.16	0.181	0.03	0.035	5.0×10^{-6}	3.0×10^{-7}	9.0×10^{-4}	6.0×10^{-5}
	1 mg/L	3.5×10^{8}	0.161	0.177	0.031	0.036	1.0×10^{-6}	2.0×10^{-7}	5.0×10^{-4}	8.0×10^{-5}
	10 mg/L	3.5×10^{8}	0.156	0.179	0.033	0.038	3.0×10^{-6}	3.0×10^{-7}	3.0×10^{-4}	5.0×10^{-5}
	50 mg/L	3.5×10^{8}	0.153	0.184	0.036	0.04	1.0×10^{-7}	6.0×10^{-7}	1.0×10^{-4}	8.0×10^{-5}
Bupropion	0.1 mg/L	4.2×10^{8}	0.159	0.182	0.036	0.037	3.0×10^{-6}	5.0×10^{-7}	5.5×10^{-4}	8.0×10^{-5}
	1 mg/L	4.2×10^{8}	0.165	0.121	0.038	0.037	4.0×10^{-6}	5.5×10^{-7}	6.4×10^{-4}	4.0×10^{-5}
	10 mg/L	4.2×10^{8}	0.153	0.132	0.032	0.038	6.5×10^{-6}	4.0×10^{-7}	5.0×10^{-4}	5.0×10^{-5}
	100 mg/L	4.2×10^{8}	0.15	0.149	0.030	0.037	5.5×10^{-6}	3.0×10^{-7}	7.0×10^{-4}	6.0×10^{-5}
Escitalopram	0.1 mg/L	3.2×10^{8}	0.158	0.161	0.032	0.039	3.6×10^{-6}	6.0×10^{-7}	6.0×10^{-4}	6.0×10^{-5}
	1 mg/L	3.2×10^{8}	0.161	0.152	0.037	0.036	5.1×10^{-6}	5.0×10^{-7}	5.0×10^{-4}	4.0×10^{-5}
	10 mg/L	3.2×10^{8}	0.159	0.185	0.036	0.036	2.0×10^{-6}	4.0×10^{-7}	5.0×10^{-4}	5.0×10^{-5}
	100 mg/L	3.2×10^{8}	0.145	0.134	0.034	0.037	4.0×10^{-6}	3.5×10^{-7}	4.0×10^{-4}	3.0×10^{-5}
Agomelatine	0.1 mg/L	4.5×10^{8}	0.151	0.190	0.037	0.037	6.0×10^{-6}	2.0×10^{-7}	3.0×10^{-4}	5.5×10^{-5}
	1 mg/L	4.5×10^{8}	0.176	0.128	0.033	0.038	2.0×10^{-6}	6.0×10^{-7}	2.0×10^{-4}	4.5×10^{-5}
	10 mg/L	4.5×10^{8}	0.161	0.124	0.034	0.038	8.0×10^{-6}	4.0×10^{-7}	6.0×10^{-4}	6.0×10^{-5}
	100 mg/L	4.5×10^{8}	0.165	0.164	0.035	0.036	6.5×10^{-6}	5.0×10^{-7}	5.0×10^{-4}	5.0×10^{-5}

Table S21 Summary of mutation rate calculated by the Luria-Delbrück fluctuation method

	Mutation rate (μ)	μ_{95-}	μ_{95+}
WT	$7.25 \pm 1.75 \times 10^{-9}$	$2.31 \pm 3.86 \times 10^{-10}$	$1.00 \pm 0.26 \times 10^{-8}$
WT_Ser (10 mg/L)	$2.00 \pm 0.29 \times 10^{-8}$	$5.56 \pm 1.09 \times 10^{-9}$	$1.73 \pm 0.32 \times 10^{-8}$

Note: μ_{95-} and μ_{95+} represent 95% confidence intervals for the mutation rate

Supplementary Texts

Text S1 Whole-genome DNA sequencing of mutant strains and single nucleotide polymorphisms (SNPs) calling

Bacterial genomic DNA was extracted by the Genomic DNA isolation kit (Sigma-Aldrich, USA) according to the manufacturer's protocol. Biological triplicate of the extracted DNA samples were submitted to Novogene Co., Ltd (Singapore) for library preparation and Illumina paired-end sequencing (HiSeq 2500, Illumina Inc, San Diego, CA). SNP calling was based on the standard best practice guide of Genome Analysis Toolkit (GATK, v4.1.4.1). Particularly, sequencing data were first converted to unmapped Binary Alignment Map (BAM) format. The sequenced reads in each sample were also mapped to *E. coli* MG1655 genome sequence (obtained from National Center for Biotechnology Information (NCBI), NC_000913.3) by mem command of BWA (v0.7.17-r1188), after which the mapped BAM files were output. Unmapped and mapped BAM files were merged and sorted by mapped coordinates, which output alignment files. Duplicates in the alignments were then marked. Duplicate marked alignments were used for the first run of SNP calling without Base Quality Score Recalibration (BQSR). BQSR is a critical pre-processing step in GATK pipeline that detects systematic sequencing errors and hence improves the accuracy of SNP calling. This step needs the known SNP sites to build a statistic model. As no such data were found for E. coli, a circling strategy was thus employed to generate such a data set. In particular, BQSR was performed using the first call as the initial known sites. Recalibrated alignments were employed for the second run of SNP calling. This procedure was repeated to obtain the stabilized fourth run of SNP calling which was used as the final set of SNP calls. Annotation of SNPs was conducted by Annovar (2019-12-06 release) (2). The obtained SNPs in each mutant strain were compared with those in the biological triplicate control group, and different nonsynonymous SNPs were regarded as where mutation happened.

Text S2 Whole-genome mRNA sequencing under the exposure of antidepressants

Bacterial total was extracted using RNeasy Mini Kit (QIAGEN®, Germany) except the protocol included an extra bead-beating step for cell lysis. Biological triplicate of the extracted RNA samples were submitted to Novogene Co., Ltd (Hong Kong, China) for library preparation and Illumina paired-end sequencing (HiSeq 2500, Illumina Inc, San Diego, CA). Gene expression levels between the antidepressant-dosed samples and the corresponding control sample were compared according to the bioinformatic pipeline. In detail, the raw sequencing data were analyzed by applying NGS QC Toolkit (v2.3.3), SeqAlto (version 0.5), and Cufflinks (version 2.2.1). The database used for alignment was the reference genome of *E. coli* MG1655 (obtained from NCBI, NC_000913.3). CummeRbund package in R was used to conduct the statistical analyses. The measure of "fragments per kilobase of a gene per million mapped reads" (FPKM) was applied to quantify gene expression. Significant differences were seen when both the p value and false discovery rate (q value) were less than 0.05.

Text S3 Genome-wide proteomic analyses under the exposure of antidepressants

Bacterial total protein was digested in S-Trap filters (ProtiFi, Huntington, USA) according to the manufacturer's procedure. The digested peptides were analyzed by the Liquid chromatography-tandem mass spectrometry (LC-MS/MS), which was performed using a Dionex Ultimate 3000 RSLCnano-LC system coupled to a Q-Exactive™ H-X Hybrid Quadrupole-Orbitrap™ mass spectrometer (Thermo Scientific™). Raw sequencing data were processed by applying Thermo Proteome Discoverer (version 2.2.0.388) towards the database of *E. coli* MG1655 (received from UniProt on 12th of July 2019). Abundance ratios of each protein between antidepressant-dosed samples and the corresponding control sample were calculated. A stringency cut-off of q value less than 0.01 was applied to identify the proteins with significantly different expression levels.

Text S4 Quantifying mathematical modeling parameters and model simulation

In detail, 1‰ of the stock bacteria solution was transferred to LB broth in a 96-well plate, containing antidepressants sertraline or duloxetine with a final concentration of 0.1, 1, 10, and 50 mg/L. LB broth without any antidepressant was the control group. The 96-well plates were then incubated at 30 °C, and OD_{600} values were measured every 10 mintues or hourly by a plate reader (CLARIOstar^{plus}, BMG Labtech, Germany). Biological triplicate experiments were conducted under each condition.

Text S5 Fluctuation test

The overnight cultured wild type *E. coli* MG1655 was diluted to 10^3 cell per mL in the fresh LB medium and 200 μL of cell suspension was uploaded onto a 96-well plate (Figure S7). The plate was covered with a plate seal to minimize evaporation and was incubated at 37 °C until the OD600 value reached 0.4~0.6. For each 96-well plate, 60 wells were pooled with cell suspension, while the border wells (36 wells) were filled with LB media only (no contamination). Among the wells with bacterial cells, 57 of the cultures were plated (the entire volume) on LB agar that contained phage vB_EcoM_LNA6 (isolated from a full-scale wastewater treatment plant in Brisbane, Australia) (3), while other 3 of the cultures were plated onto LB agar without phage to enumerate the total cell number. The cultures were mixed with phage in agarose before pooling onto the LB agar plates. All the plates were incubated for 1-2 days at 37 °C until colonies were large enough to count. Each plate was run in biological triplicate.

References:

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3. Ngiam L, Weynberg KD, & Guo J (2022) The presence of plasmids in bacterial hosts alters phage isolation and infectivity. *ISME Communications* 2(1):1-11.