

Concomitant drugs associated with increased mortality for MDMA users reported in a drug safety surveillance database

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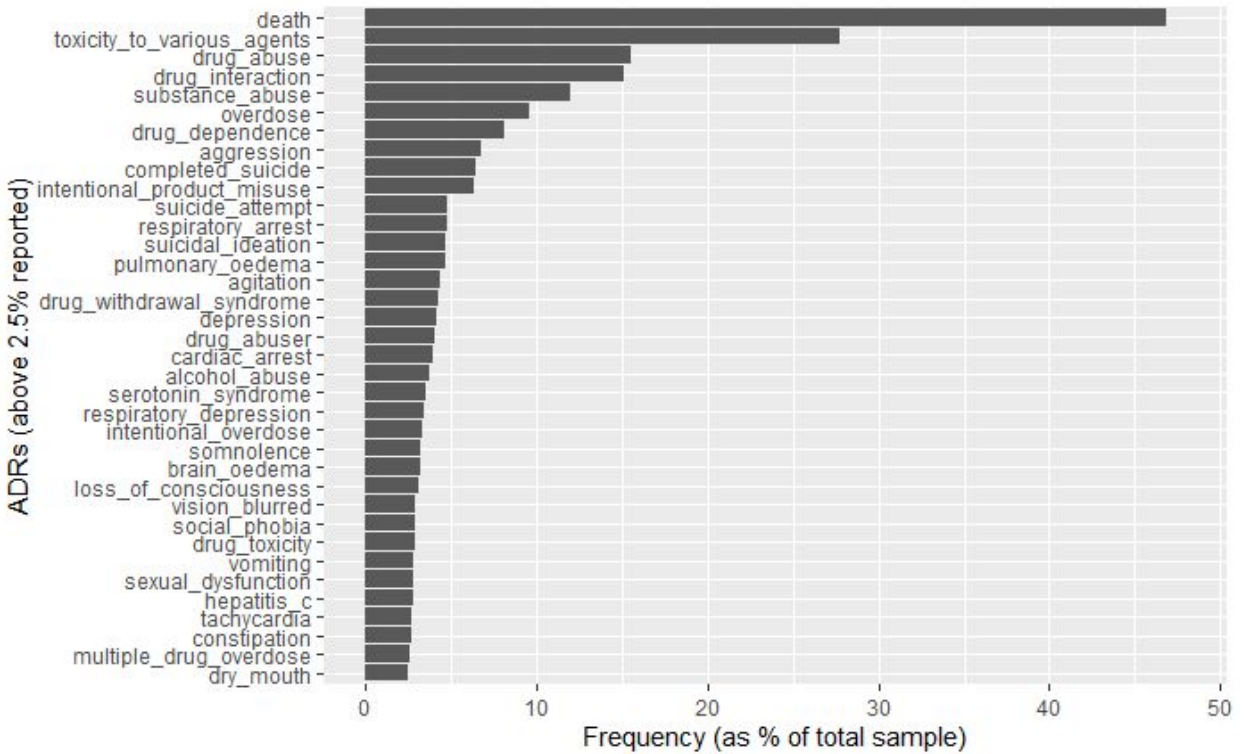
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Supplementary information

Figure S1. Frequency of most common side effects



Supp. Figure 1 Legend. Frequency of occurrence of the most common side effects in the dataset (above 2.5%).

Table S1. Univariate Unadjusted Odds Ratios for Odds of Death

Class Name	OR	95%CI-Lo	95%CI-Hi
Opioids	1.20	1.08	1.34
Antidepressants	0.93	0.80	1.08
Benzodiazepines	1.80	1.54	2.14
Amphetamines & Stimulants	2.23	1.82	2.76
Cannabinoids	0.59	0.45	0.77
Antipsychotics	0.74	0.58	0.92
Cocaine	0.37	0.27	0.50
Non-Opioids for Pain	0.68	0.51	0.90
Dissociative Anesthetics	1.31	0.95	1.83
Psychedelics	0.31	0.18	0.51
Anesthetics	3.14	1.94	5.84
HIV	0.33	0.13	0.58
AEDs	0.81	0.54	1.15
Sedative Hypnotics	0.93	0.63	1.37
Ethanol	1.46	0.87	2.47
Antimicrobials	0.13	0.03	0.35
MDMA Metab. & Analogs	18.56	5.70	114.16
Muscle Relaxants	2.62	1.24	6.21
*Lithium	NA	NA	NA
Nicotine	0.06	0.01	0.21
Anticholinergic	0.73	0.42	1.25

Supp. Table 1 Legend. Univariate unadjusted odds ratios for risk of death per additional drug added on from each class. 95% Confidence intervals reported. Odds Ratios (OR) greater than 1 indicate increased risk of death. Odds Ratios less than 1 indicate decreased risk of death. (*Note that the OR for Lithium is incalculable due to no occurrences of death in the study).

Table S2. Drugs Included in Study and their Drug Class Assignments

Drug Class	Drug Name
<i>AED</i>	pregabalin
<i>AED</i>	lamotrigine
<i>AED</i>	valproic_acid
<i>AED</i>	gabapentin
<i>AED</i>	levetiracetam
<i>AED</i>	topiramate
<i>AED</i>	briviact
<i>AED</i>	depamide
<i>AED</i>	lacosamide
<i>AED</i>	phenytoin
<i>AED</i>	carbamazepine
<i>AED</i>	oxcarbazepine
<i>Amphetamines & Stimulants</i>	methamphetamine
<i>Amphetamines & Stimulants</i>	amphetamine
<i>Amphetamines & Stimulants</i>	methylphenidate
<i>Amphetamines & Stimulants</i>	amfetamine
<i>Amphetamines & Stimulants</i>	methylenedioxyamphetamine
<i>Amphetamines & Stimulants</i>	amphetamines
<i>Amphetamines & Stimulants</i>	metamfetamine
<i>Amphetamines & Stimulants</i>	pseudoephedrine
<i>Amphetamines & Stimulants</i>	adderall
<i>Amphetamines & Stimulants</i>	amphetamine,dextroamphetamine
<i>Amphetamines & Stimulants</i>	dextroamphetamine_and_amphetamine_salts
<i>Amphetamines & Stimulants</i>	modafinil
<i>Amphetamines & Stimulants</i>	amfetamine_sulfate
<i>Amphetamines & Stimulants</i>	atomoxetine
<i>Amphetamines & Stimulants</i>	centrally_acting_sympathomimetics
<i>Amphetamines & Stimulants</i>	ibuprofen,pseudoephedrine
<i>Amphetamines & Stimulants</i>	actifed
<i>Amphetamines & Stimulants</i>	armodafinil
<i>Amphetamines & Stimulants</i>	cathinone
<i>Amphetamines & Stimulants</i>	cathinone_derivatives_no_pref_name
<i>Amphetamines & Stimulants</i>	ephedrine
<i>Amphetamines & Stimulants</i>	mcat
<i>Amphetamines & Stimulants</i>	mephedrone
<i>Amphetamines & Stimulants</i>	n_methylephedrone
<i>Amphetamines & Stimulants</i>	paramethoxymethamphetamine_no_pref_name

<i>Amphetamines & Stimulants</i>	ritaline
<i>Amphetamines & Stimulants</i>	speed
<i>Amphetamines & Stimulants</i>	3_fluorophenmetrazine
<i>Amphetamines & Stimulants</i>	4_mec
<i>Amphetamines & Stimulants</i>	4_methyl_n_ethyl_pentdrone
<i>Amphetamines & Stimulants</i>	4_methylmethcathinone
<i>Amphetamines & Stimulants</i>	amphetamine_no_pref_name
<i>Amphetamines & Stimulants</i>	amphetamine_salts_amfetamine_salts
<i>Amphetamines & Stimulants</i>	amphetamine_salts_no_pref_name
<i>Amphetamines & Stimulants</i>	crystal_methamphetamine
<i>Amphetamines & Stimulants</i>	epinephrine
<i>Amphetamines & Stimulants</i>	lisdexamfetamine
<i>Amphetamines & Stimulants</i>	metamfetamine_hcl
<i>Amphetamines & Stimulants</i>	metamphetamine
<i>Amphetamines & Stimulants</i>	methamphetamine_no_pref_name
<i>Amphetamines & Stimulants</i>	methamphetamines
<i>Amphetamines & Stimulants</i>	methylamphetamine
<i>Amphetamines & Stimulants</i>	norepinephrine
<i>Amphetamines & Stimulants</i>	phentermine
<i>Amphetamines & Stimulants</i>	phenylephrine
<i>Amphetamines & Stimulants</i>	stimulants
<i>Anesthetics</i>	epinephrine,lidocaine
<i>Anesthetics</i>	rocuronium
<i>Anesthetics</i>	anesthetics
<i>Anesthetics</i>	benzocaine
<i>Anesthetics</i>	bupivacaine
<i>Anesthetics</i>	local_anesthetics
<i>Anesthetics</i>	procaine
<i>Anesthetics</i>	suxamethonium
<i>Anesthetics</i>	vecuronium
<i>Anticholinergic</i>	diphenhydramine
<i>Anticholinergic</i>	promethazine
<i>Anticholinergic</i>	diphenhydramine,zinc
<i>Anticholinergic</i>	trihexyphenidyl
<i>Anticholinergic</i>	atropine
<i>Anticholinergic</i>	dimenhydrinate
<i>Anticholinergic</i>	benzatropine
<i>Anticholinergic</i>	acetaminophen,diphenhydramine
<i>Anticholinergic</i>	donormyl

<i>Anticholinergic</i>	donormyl doxylamine sodium bromide sodium phosphate dibasic sodium sulfate
<i>Anticholinergic</i>	scopolamine
<i>Anticholinergic</i>	tiotropium
<i>Antidepressants</i>	fluoxetine
<i>Antidepressants</i>	venlafaxine
<i>Antidepressants</i>	citalopram
<i>Antidepressants</i>	paroxetine
<i>Antidepressants</i>	bupropion
<i>Antidepressants</i>	lofepramine
<i>Antidepressants</i>	sertraline
<i>Antidepressants</i>	mirtazapine
<i>Antidepressants</i>	desvenlafaxine
<i>Antidepressants</i>	antidepressants
<i>Antidepressants</i>	trazodone
<i>Antidepressants</i>	seroxat_smith_kline_beecham
<i>Antidepressants</i>	escitalopram
<i>Antidepressants</i>	dothiepin_hcl
<i>Antidepressants</i>	moclobemide
<i>Antidepressants</i>	reboxetine
<i>Antidepressants</i>	dothiepin_00160401
<i>Antidepressants</i>	doxepin
<i>Antidepressants</i>	duloxetine
<i>Antidepressants</i>	amitriptyline
<i>Antidepressants</i>	antidepressant_nos
<i>Antidepressants</i>	desipramine
<i>Antidepressants</i>	dothiepin
<i>Antidepressants</i>	efexor
<i>Antidepressants</i>	nortriptylin
<i>Antidepressants</i>	phenelzine
<i>Antidepressants</i>	ratio_venlafaxine
<i>Antidepressants</i>	selective_serotonin_reuptake_inhibitor
<i>Antidepressants</i>	sertralin_01011402
<i>Antidepressants</i>	st_john_s_wort
<i>Antidepressants</i>	tricyclic_antidepressants
<i>Antimicrobials</i>	clarithromycin
<i>Antimicrobials</i>	azithromycin
<i>Antimicrobials</i>	clindamycin
<i>Antimicrobials</i>	glecaprevir,pibrentasvir
<i>Antimicrobials</i>	fluconazole

<i>Antimicrobials</i>	levamisole
<i>Antimicrobials</i>	sulfamethoxazole,trimethoprim
<i>Antimicrobials</i>	amoxicillin
<i>Antimicrobials</i>	cephalexin
<i>Antimicrobials</i>	doxycycline
<i>Antimicrobials</i>	pentamidine
<i>Antimicrobials</i>	telithromycin
<i>Antimicrobials</i>	aciclostad
<i>Antimicrobials</i>	amoxi_1a_pharma
<i>Antimicrobials</i>	amoxicillin,clavulanate
<i>Antimicrobials</i>	ceftriaxon_actavis
<i>Antimicrobials</i>	doxycyclin_00055701
<i>Antimicrobials</i>	fluconazole_in_sodium_chloride_injection_usp
<i>Antimicrobials</i>	fluoroquinolones
<i>Antimicrobials</i>	magistrale
<i>Antimicrobials</i>	moxifloxacin
<i>Antimicrobials</i>	nitrofurantoin
<i>Antipsychotics</i>	olanzapine
<i>Antipsychotics</i>	aripiprazole
<i>Antipsychotics</i>	quetiapine
<i>Antipsychotics</i>	metoclopramide
<i>Antipsychotics</i>	clozapine
<i>Antipsychotics</i>	risperidone
<i>Antipsychotics</i>	chlorpromazine
<i>Antipsychotics</i>	cyamemazine
<i>Antipsychotics</i>	haloperidol
<i>Antipsychotics</i>	propiomazine
<i>Antipsychotics</i>	prochlorperazine
<i>Antipsychotics</i>	ziprasidone
<i>Antipsychotics</i>	domperidone
<i>Antipsychotics</i>	fluphenazine
<i>Antipsychotics</i>	paliperidone
<i>Antipsychotics</i>	quetiapin
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<i>Antipsychotics</i>	amisulpride
<i>Antipsychotics</i>	antipsychotics
<i>Antipsychotics</i>	chlorprothixene
<i>Antipsychotics</i>	dominal

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<i>Benzodiazepines</i>	oxazepam
<i>Benzodiazepines</i>	temazepam
<i>Benzodiazepines</i>	lorazepam
<i>Benzodiazepines</i>	nordazepam
<i>Benzodiazepines</i>	midazolam
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<i>Benzodiazepines</i>	tavor
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<i>Cannabinoids</i>	marijuana
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<i>Cannabinoids</i>	thc_no_pref_name
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<i>Cannabinoids</i>	ab_fubinaca
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<i>HIV</i>	raltegravir
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<i>HIV</i>	tenofovir
<i>HIV</i>	zidovudine
<i>HIV</i>	acyclovir
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<i>HIV</i>	nevirapine
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<i>HIV</i>	dolutegravir
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<i>HIV</i>	emtricitabine_tenofovir_disoproxil_tenofovir_disoproxil_fumarate
<i>HIV</i>	eviplera
<i>HIV</i>	rilpivirine
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<i>Muscle_Relaxant</i>	methocarbamol
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<i>Nicotine</i>	tabac_poudre_de
<i>Nicotine</i>	tabacum
<i>Nicotine</i>	varenicline
<i>NonOpioid_Pain</i>	acetaminophen
<i>NonOpioid_Pain</i>	ibuprofen
<i>NonOpioid_Pain</i>	aspirin
<i>NonOpioid_Pain</i>	diclofenac
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<i>NonOpioid_Pain</i>	naproxen
<i>NonOpioid_Pain</i>	paracetamol
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<i>NonOpioid_Pain</i>	nuprofen
<i>Opioids</i>	methadone
<i>Opioids</i>	morphine
<i>Opioids</i>	codeine
<i>Opioids</i>	oxycodone

<i>Opioids</i>	heroin
<i>Opioids</i>	buprenorphine
<i>Opioids</i>	fentanyl
<i>Opioids</i>	acetaminophen,oxycodone
<i>Opioids</i>	tramadol
<i>Opioids</i>	hydromorphone
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<i>Opioids</i>	dihydrocodeine
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<i>Opioids</i>	opiods
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<i>Opioids</i>	opium_morphine
<i>Opioids</i>	oramorph_sr_sustained_release
<i>Opioids</i>	oxycontin_talbets_oxycodone_hcl
<i>Opioids</i>	oxymorphone
<i>Opioids</i>	panlor
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<i>Opioids</i>	remifentanil
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<i>Psychedelics</i>	lsd
<i>Psychedelics</i>	lysergide
<i>Psychedelics</i>	lysergic_acid_diethylamide
<i>Psychedelics</i>	psilocybine
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<i>Psychedelics</i>	hallucinogenic_mushroom
<i>Psychedelics</i>	lsd_tartrate_de
<i>Psychedelics</i>	lysergic_acid_diethylamide_lsd
<i>Psychedelics</i>	mushroom
<i>Psychedelics</i>	mushroom_tea_psilocybine
<i>Psychedelics</i>	mushrooms
<i>Psychedelics</i>	other_psychostimulants_and_nootropics
<i>Psychedelics</i>	lsd_25
<i>Sedative Hypnotics</i>	zolpidem
<i>Sedative Hypnotics</i>	ghb

<i>Sedative Hypnotics</i>	gamma_hydroxybutyrate
<i>Sedative Hypnotics</i>	melatonin
<i>Sedative Hypnotics</i>	zopiclone
<i>Sedative Hypnotics</i>	gamma_butyrolactone
<i>Sedative Hypnotics</i>	oxybate_sodium
<i>Sedative Hypnotics</i>	clonidine
<i>Sedative Hypnotics</i>	phenobarbital
<i>Sedative Hypnotics</i>	zaleplon
<i>Sedative Hypnotics</i>	barbiturates_and_derivatives
<i>Sedative Hypnotics</i>	sleeping_pills
<i>Sedative Hypnotics</i>	ximovan
<i>Sedative Hypnotics</i>	gamma_hydroxybutyric_acid_ecstasy
<i>Sedative Hypnotics</i>	sodium_oxybate

Table S3. Multivariate Adjusted Odds Ratios for Odds of Death

Class Name	aOR	95%CI-Lo	95%CI-Hi
Opioids	1.31	1.11	1.55
Antidepressants	1.67	1.31	2.16
Benzodiazepines	1.75	1.42	2.19
Amphetamines & Stimulants	2.21	1.69	2.94
Cannabinoids	0.37	0.25	0.54
Antipsychotics	0.42	0.28	0.61
Cocaine	0.41	0.28	0.60
Dissociative Anesthetics	1.37	0.93	2.06
Psychedelics	0.25	0.12	0.48
Anesthetics	2.95	1.56	6.49
HIV	0.40	0.15	0.75
AEDs	0.49	0.29	0.80
Sedative Hypnotics	0.61	0.34	1.06
Ethanol	1.98	1.03	3.94
Antimicrobials	0.07	0.01	0.27
MDMA Metab. & Analogs	7.11	1.99	45.81
Muscle Relaxants	10.61	3.51	35.97
*Lithium	NA	NA	NA
Nicotine	0.08	0.01	0.31

Supp. Table S3 Legend. Multivariate adjusted odds ratios for risk of death per additional drug added on from each class. 95% Confidence intervals reported. Adjusted Odds Ratios (aOR) greater than 1 indicate increased risk of death. Adjusted Odds Ratios less than 1 indicate decreased risk of death. (*Note that the aOR for Lithium is incalculable due to no occurrences of death in the study).

Table S4. Multivariate Adjusted Odds Ratios for Odds of Death, Binary Predictors

Class Name	aOR	95%CI-Lo	95%CI-Hi
Opioids	2.05	1.46	2.90
Antidepressants	1.62	1.11	2.36
Benzodiazepines	2.25	1.61	3.15
Amphetamines & Stimulants	3.05	2.13	4.41
Cannabinoids	0.33	0.22	0.48
Antipsychotics	0.40	0.25	0.62
Cocaine	0.42	0.28	0.62
Dissociative Anesthetics	1.42	0.83	2.45
Psychedelics	0.26	0.13	0.50
Anesthetics	7.13	2.37	26.93
HIV	0.10	0.01	0.38
AEDs	0.83	0.44	1.54
Sedative Hypnotics	0.78	0.43	1.40
Ethanol	2.03	1.06	3.99
Antimicrobials	0.06	0.01	0.27
MDMA Metab. & Analogs	8.71	2.46	55.49
Muscle Relaxants	8.17	2.87	25.98
*Lithium	NA	NA	NA
Nicotine	0.09	0.01	0.35

Supp. Table S4 Legend. Multivariate adjusted odds ratios for risk of death associated with each drug class (coded as a binary predictor). 95% Confidence intervals reported. Adjusted Odds Ratios (aOR) greater than 1 indicate increased risk of death. Adjusted Odds Ratios less than 1 indicate decreased risk of death. (*Note that the aOR for Lithium is incalculable due to no occurrences of death in the study).

Table S5. Univariate Odds Ratios for Odds of Death, Antidepressants

Class Name	OR	95%CI-Lo	95%CI-Hi
bupropion (n= 40)	2.82	1.43	5.96
paroxetine (n= 53)	0.17	0.07	0.34
fluoxetine (n= 62)	0.20	0.10	0.38
venlafaxine (n= 66)	1.97	1.19	3.36
citalopram (n= 56)	1.92	1.10	3.42
lofepramine (n= 30)	0.11	0.03	0.31
sertraline (n=26)	2.36	1.05	5.80
mirtazapine (n= 19)	0.36	0.12	0.95

Supp. Table S5 Legend. Univariate unadjusted odds ratios for risk of death with each individual antidepressant. 95% Confidence intervals reported. Odds Ratios greater than 1 indicate increased risk of death. Odds Ratios less than 1 indicate decreased risk of death.

Table S6. Univariate Odds Ratios for Odds of Death, Antipsychotics

Class Name	OR	95%CI-Lo	95%CI-Hi
olanzapine (n= 71)	1.86	1.13	3.10
aripiprazole (n= 33)	0.07	0.01	0.22
quetiapine (n= 54)	0.64	0.41	0.97
*metoclopramide (n=18)	NA	NA	NA
clozapine (n= 11)	0.10	0.01	0.53
*risperidone (n= 11)	NA	NA	NA

Supp. Table S6 Legend. Univariate unadjusted odds ratios for risk of death with each individual antipsychotic. 95% Confidence intervals reported. Odds Ratios greater than 1 indicate increased risk of death. Odds Ratios less than 1 indicate decreased risk of death. (*Note that the odds ratio for metoclopramide is incalculable due to no occurrences of survival in the study, conversely the odds ratio for risperidone is incalculable due to no occurrences of death during the study).