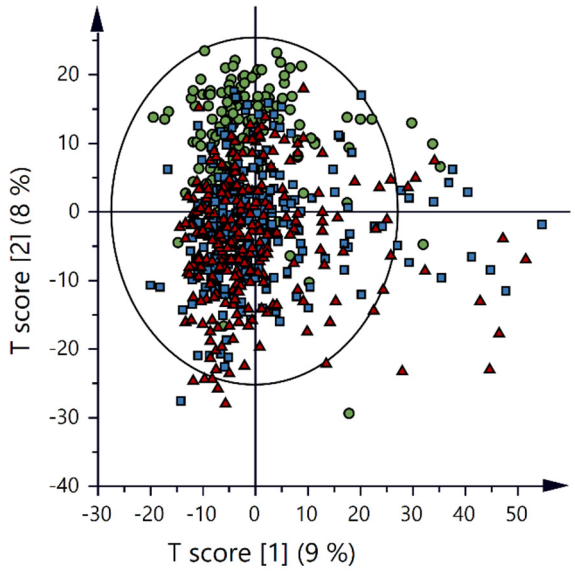

Figure S1. ***PCA score plot.*** *Oxycodone intoxications (n=249, ▲), positive controls (n=244, ■) and negative controls (n=132, ●)(R2 = 0.61, Q2 = 0.54).*

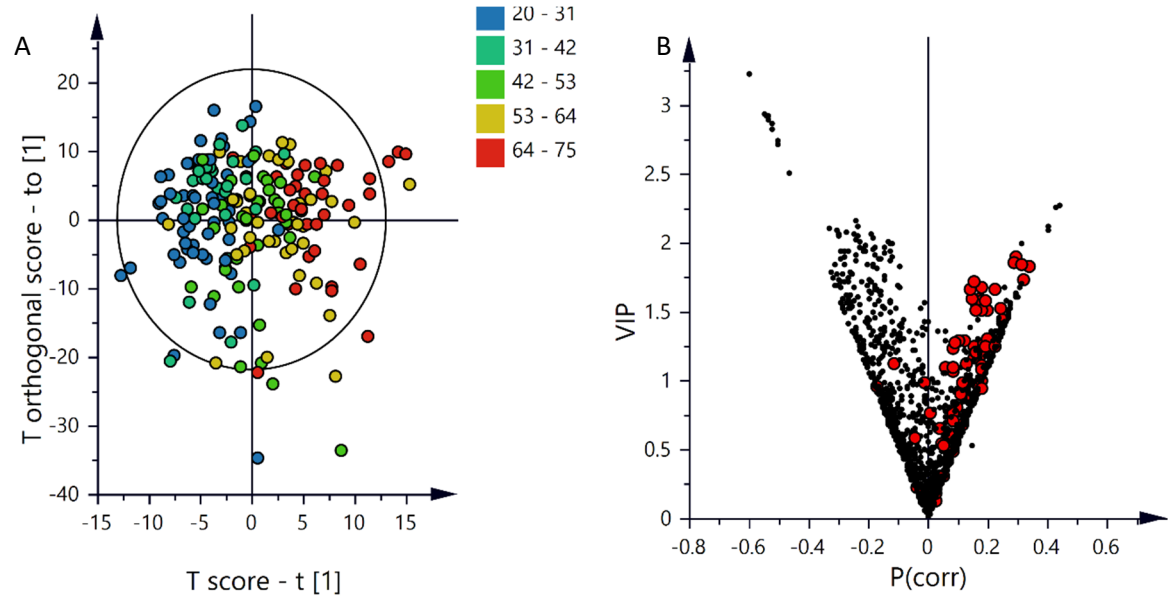

Figure S2. ***Age based OPLS model.*** *Figure A is a color coded scoreplot illustrating age related correlations(blue=20-31 years, turquoise=31-42 years , green=42-53 years, yellow=53-64 years, red=64-75 years). The model is based on all autopsy cases from the negative controls (n=195). Figure B is a corresponding volcanoplot, illustrating how acylcarnitines (red circles) impact and correlates with age. Some acylcarntine has a positive corraltion, however the model impact and the correlation is poor (p(corr)<0,2, VIP<1.5), in comparison to acylcarnitines correlation to intoxication. For comparison see Figure 2, Figures S3, S4and S5.*

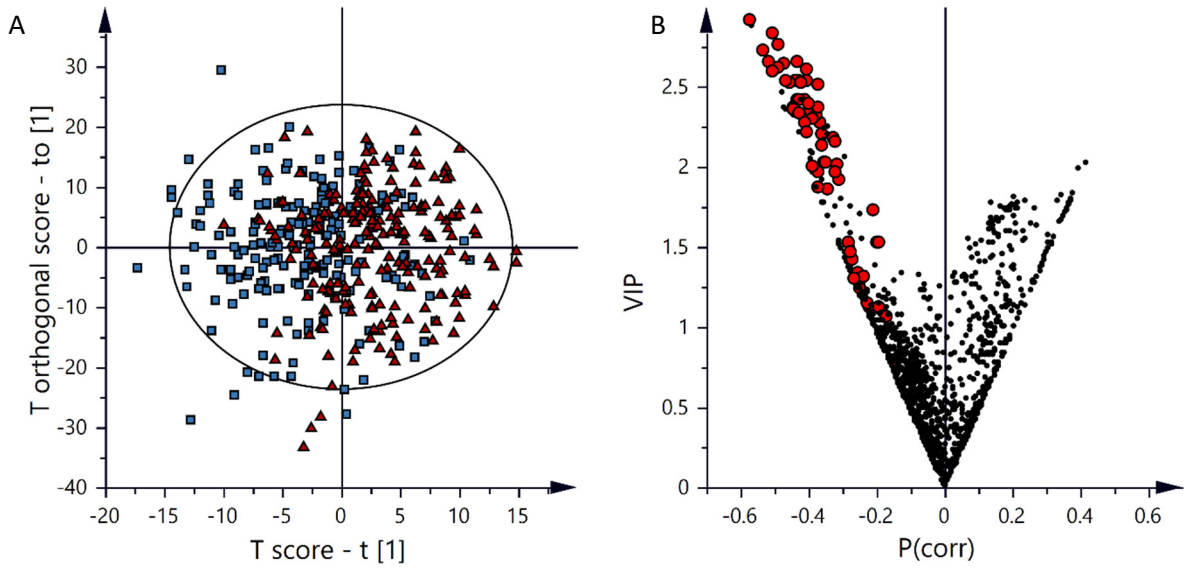

Figure S3. ***Age-matched OPLS-DA model.*** *In the age matched OPLS-DA score plot (A), a trend in group separation on a population level is still observed between oxycodone intoxications (n = 207, mean age = 56,▲) and the positive controls (n = 192, mean age = 56, ■). In addition, a volcanoplot (B) illustrates that acylcarnitines (red circeles) are of high importance for the trend in group separation, where a majority has a p(corr) < -0.2 and VIP > 1,5 (R2 = 0.28, Q2 = 0.12).*

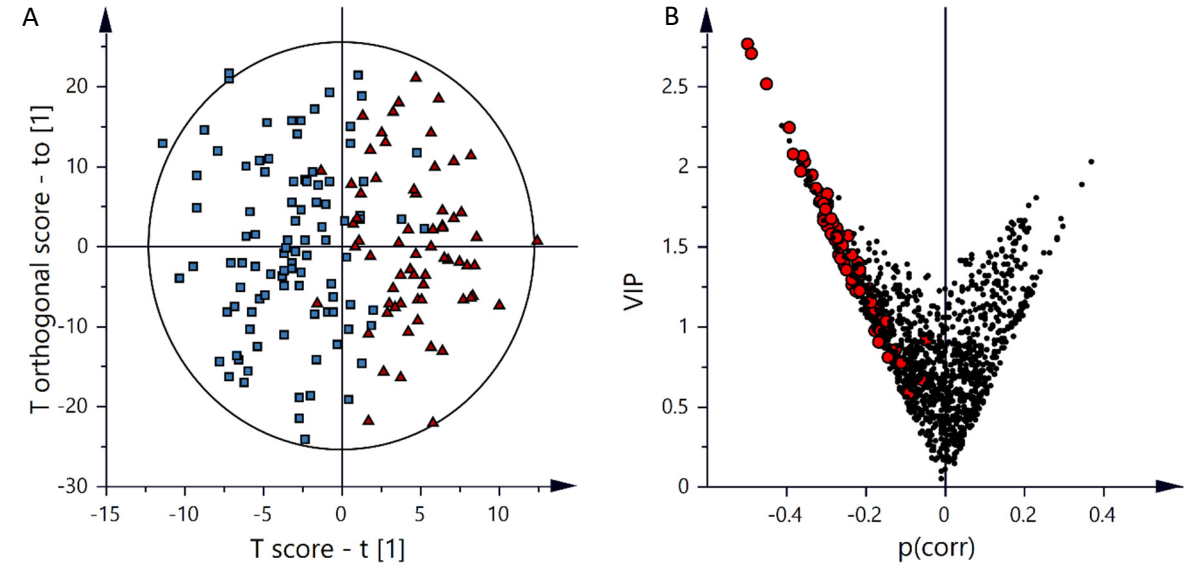

Figure S4. ***Age and PMI-matched OPLS-DA model.*** *In the age and PMI matched OPLS-DA score plot (A), a stronger trend in group separation on a population level is observed between oxycodone intoxications (n = 66, ▲) and the positive controls (n =96, ■). In addition, a volcanoplot (B) illustrates that acylcarnitines (red circeles) still are of high importance for the trend in group separation, where a majority has a p(corr) < -0.2 and VIP > 1,5. Mean age and mean PMI were comparable between the groups (p = 0,72 and 0,35 respectively). Sensitivity and specificity for the model were above 90 % however the Q2 were low (R2 = 0.61, Q2 = 0.08).*

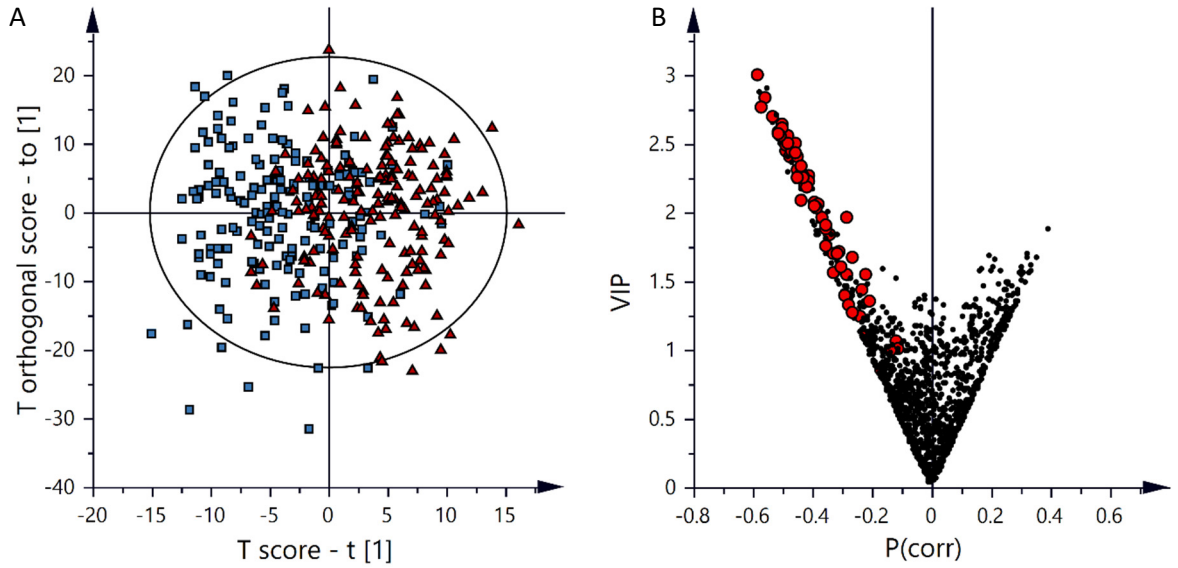

Figure S5. ***Modified OPLS-DA model with regard to decomposition.*** *Overview of OPLS-DA model without autopsy cases with tendency of decomposition. In the OPLS-DA score plot (A), a similat trend in group separation on a population level is observed between oxycodone intoxications (▲) and the positive controls (■) in comparison to the model including the whole training set (Figure 1). In addition, a volcanoplot (B) illustrates that acylcarnitines (red circeles) are of high importance for group separation, where a majority has a p(corr) < -0.2 and VIP > 1,5 (R2 = 0.42, Q2 = 0.26).*

Table S1. Demographic overview of detected CNS-depressant drugs in the three study groups.

Analyte[1]	Intoxications (n=376)	Positive Controls (n=364)	Negative Controls (n=207)
Negative drug screening	0%	0%	42%
Ethanol	30%	16%	36%
Alprazolam	26%	10%	5%
Buprenorphine	4%	1%	1%
Buspirone	1%	0%	1%
Clomethiazole	0%	0%	0%
Clonazepam	3%	1%	0%
Clozapine	1%	0%	0%
Dexmedetomidine	1%	1%	0%
Diazepam	26%	9%	7%
Fentanyl	4%	10%	0%
Haloperidol	1%	2%	1%
Hydromorphone	0%	0%	0%
Hydroxyzine	5%	4%	2%
Ketobemidone	1%	0%	0%
Levomepromazine	3%	1%	1%
Lithium	0%	0%	0%
Lorazepam	1%	1%	0%
Methadone	5%	1%	0%
Midazolam	1%	4%	0%
Morphine	11%	9%	1%
Nitrazepam	1%	1%	1%
Olanzapine	3%	2%	6%
Oxazepam	13%	9%	5%
Oxycodone	100%	100%	0%
Propiomazine	7%	2%	1%
Risperidone	1%	1%	1%
Tapentadol	1%	0%	0%
Tramadol	9%	4%	1%
Zolpidem	11%	5%	1%
Zopiclone	29%	20%	7%

Table S2. Cause of Death and Analytical Findings for False positives and False neagiteves (t>5 or t<-5).

Classified as Control predicted as Intoxication	Primary Cause of Death	Secondary Cause of Death	Positive analytes
Positive Control 1	Old myocardial infarction	Alcohol dependence syndrome	0,01 µg/g alprazolam 0,5 µg/g oxycodone 2,5 µg/g venlafaxine 11 µg/g lamotrigine 0,37 µg/g O-desmethylvenlafaxine 0,36 µg/g mirtazapine 0,03 µg/g desmethylmirtazapine 0,08 µg/g duloxetine
Positive Control 2	Hanging	Poisoning by other and unspecified drugs and medicinal substances	0,24 µg/g alprazolam

			0,34 µg/g Amphetamine 0,25 µg/g diazepam 0,12 µg/g nordazepam 9,3 µg/g ketamine 0,18 µg/g 7-amino-clonazepam 0,54 µg/g MDMA 0,05 µg/g oxazepam 7,1 µg/g oxycodone 0,6 µg/g propranolol 0,04 µg/g temazepam 0,06 µg/g zopiclone 0,03 µg/g zolpidem 0,67 ‰ ethanol i lårblod 0,45 µg/g norfludiazepam 55 ng/g Cyclopropylfentanyl
Positive Control 3	Ill-defined descriptions and complications of heart disease	Drug dependence	0,39 µg/g alimemazine 0,13 µg/g desmethylalimemazine 0,02 µg/g alprazolam 0,5 µg/g oxycodone 1,2 µg/g venlafaxine 0,16 µg/g O-desmethylvenlafaxine 6,4 µg/g pregabalin 0,13 ‰ ethanol i lårblod
Positive Control 4	Hanging		0,83 µg/g citalopram 0,27 µg/g desmethylcitalopram 0,08 µg/g diazepam 0,14 µg/g nordazepam 0,5 µg/g oxycodone 0,05 µg/g propiomazine 0,19 µg/g dihydropropiomazine 0,03 µg/g zopiclone 7,5 µg/g tramadol 1,2 µg/g O-desmethyltramadol 11 µg/g pregabalin 0,20 µg/g amlodipine 0,07 µg/g melatonin
Positive Control 5	Toxic effect of carbon monoxide		0,33 µg/g diazepam 0,06 µg/g nordazepam 47 % carboxyhemoglobin 0,24 µg/g oxazepam

			0,03 µg/g oxycodone 4,4 µg/g lamotrigine 0,68 µg/g bupropion 0,54 µg/g duloxetine 0,27 µg/g hydroxybupropion 1,26 ‰ ethanol
Classified as Intoxication, Predicted as Positive Control	**Primary Cause of Death**	**Secondary Cause of Death**	**Positive analytes**
Inoxication 6	Toxic effect of alcohol	Diseases of esophagus	0,006 µg/g oxycodone 3,69 ‰ ethanol
Inoxication 7	Poisoning by other and unspecified drugs and medicinal substances (Multiple organ failure)		8,9 µg/g furosemide 0,01 µg/g codeine 0,05 µg/g midazolam 0,08 µg/g oxycodone 54 µg/g acetaminophen
Inoxication 8	Poisoning by other and unspecified drugs and medicinal substances		0,07 µg/g 7-amino-clonazepam 0,0023 µg/g clonidine 0,03 µg/g midazolam 0,14 µg/g morphine 0,07 µg/g oxazepam 0,006 µg/g oxycodone 14 µg/g acetaminophen 0,0003 µg/g dexmedetomidine
Inoxication 9	Poisoning by other and unspecified drugs and medicinal substances		0,48 µg/g amphetamine 0,80 µg/g citalopram 0,05 µg/g desmethylcitalopram 0,3 µg/g oxycodone 67 µg/g acetaminophen 0,55 µg/g cetirizine 2,7 µg/g pregabalin
Inoxication 10	Poisoning by other and unspecified drugs and medicinal substances	Chronic obstructive pulmonary disease	0,36 µg/g alimemazine 0,07 µg/g desmethylalimemazine 0,82 µg/g citalopram

			0,06 µg/g desmethylcitalopram 0,009 µg/g clonazepam 0,23 µg/g 7-amino-clonazepam 0,12 µg/g oxycodone 17 µg/g acetaminophen 0,06 µg/g dihydropropiomazine 0,03 µg/g zolpidem 14 µg/g gabapentin
Inoxication 11	Poisoning by other and unspecified drugs and medicinal substances	Other forms of chronic ischemic heart disease	0,15 µg/g alimemazine 0,13 µg/g desmethylalimemazine 0,02 µg/g oxycodone 0,53 µg/g zopiclone
Inoxication 12	Poisoning by other and unspecified drugs and medicinal substances		0,28 µg/g citalopram 0,15 µg/g desmethylcitalopram 0,07 µg/g diazepam 0,07 µg/g nordazepam 11 ng/g fentanyl 0,01 µg/g oxycodone 0,15 µg/g dihydropropiomazine 1,7 µg/g trimetoprim 0,19 µg/g quetiapine 0,05 µg/g zolpidem 0,21 µg/g mirtazapine 0,09 µg/g desmethylmirtazapine 25 µg/g gabapentin

Table S3. Demographic overview of training set and validations set for study cohort.

	Oxycodone intoxications		Positive Controls		Negative Controls	
	Training	Validation	Training	Validation	Training	Validation
n	249	126	244	120	132	63
Females/males	116/133	44/82	77/167	46/74	29/103	15/48
Age (yrs)	48 (36-62)	46 (34-57)	64 (52-72)	67 (57-77)	49 (30-60)	45 (29-56)
Body weight (kg)	85 (71-99)	87 (73-104)	76 (62-92)	74 (62-91)	73 (65-83)	74 (62-91)
Body Height (cm)	173 (165-181)	174 (166-182)	173 (165-180)	172 (166-179)	175 (170-180)	172 (166-179)
Body Mass Index (kg/m^2)	29 (25-33)	29 (25-34)	26 (22-30)	25 (22-29)	24 (22-27)	25 (22-29)