Supplemental Figure and Tables

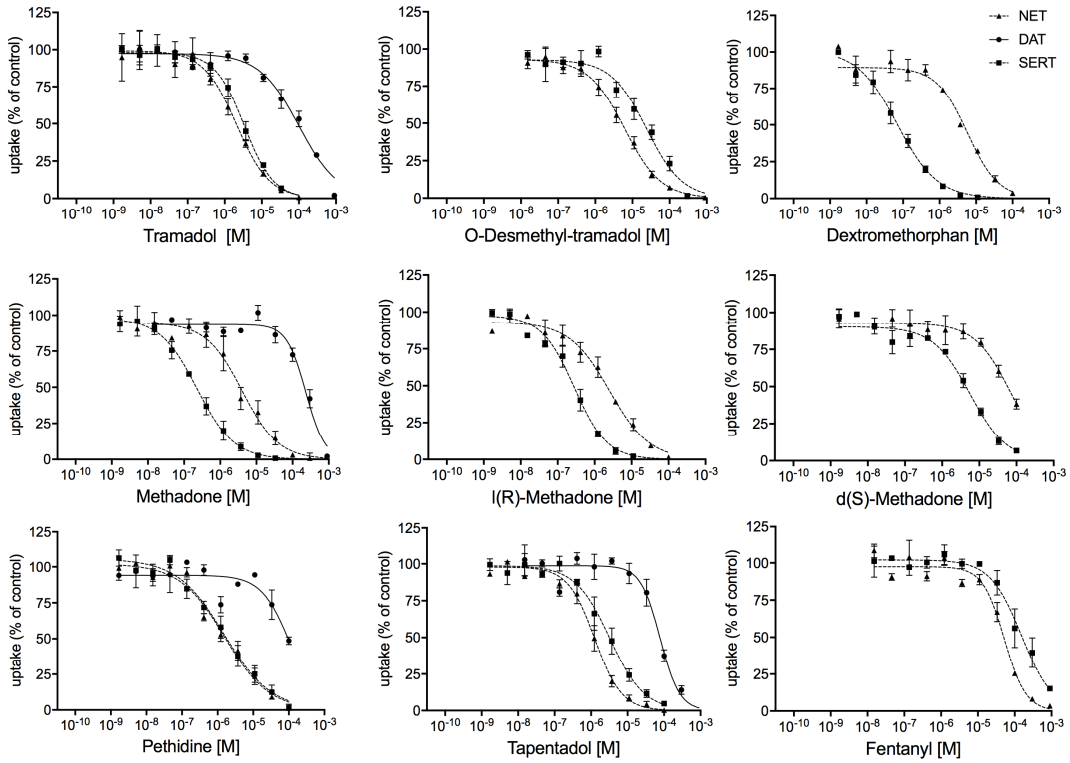

Figure S1. Monoamine uptake inhibition in stably transfected HEK 293 cells that expressed the human NET, DAT, or SERT. The data are presented as the mean ± SEM of three independent experiments. Curves were fitted by non-linear regression, and corresponding IC_{50} values are shown in Table 1. DAT inhibition curves were not performed for substances that did not inhibit the DAT at 100 µM.

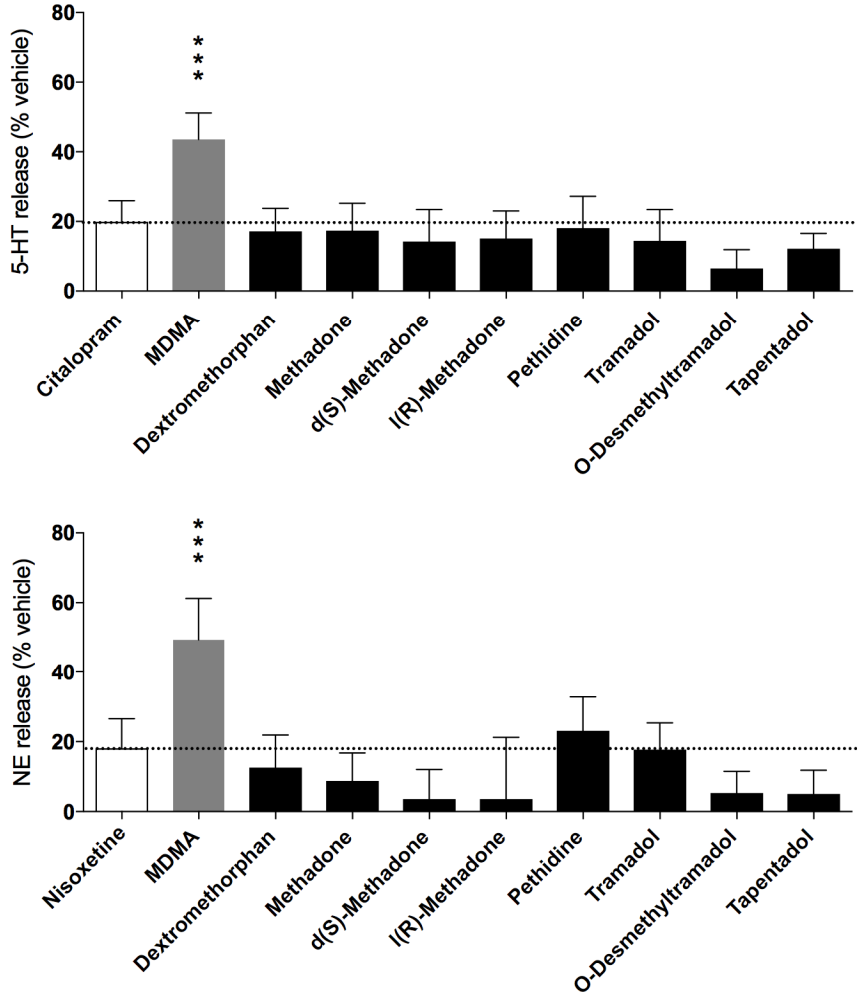

Figure S2. None of the opioids released serotonin (5-HT) or norepinephrine (NE). Monoamine release was induced by 100 µM of the compounds after preloading HEK 293 cells that expressed the human NET or SERT with radiolabeled monoamine. The dashed line marks nonspecific "pseudo-efflux" that arises from monoamine diffusion and subsequent reuptake inhibition. Substances that caused significantly more monoamine efflux (***p < 0.001) than non-releasing uptake inhibitors (open bars) were determined to be monoamine releasers. 3,4-Methylenedioxymethamphetamine (MDMA) served as positive control known to release 5-HT and NE. There was a significant main effect of 5-HT and NE release ($F_{9,64}$=89.13, P<0.001 and $F_{10,78}$=21.46, P<0.001, respectively) but only the positive control MDMA induced significantly greater 5-HT and NE release compared with citalopram and nisoxetine (both P<0.001), respectively. The data are presented as the mean and SEM of five independent experiments.

Table S1. Cases of opioid-associated serotonin syndrome reported by PubMed

	Single (daily) doses	References
Tramadol	-100 mg p.o. 4/d (400) -50 mg p.o. 10/d (500) -100 mg p.o. 3/d (300) -50 mg p.o. 4/d (150-200) -750 mg p.o. (750) overdose 100 mg p.o. 3/d (300) -(150 mg p.o.) -100 mg p.o. single dose	(Lantz *et al.*, 1998; Kesavan *et al.*, 1999; Gonzalez-Pinto *et al.*, 2001; Lange-Asschenfeldt *et al.*, 2002; Houlihan, 2004; leDoux *et al.*, 2004; Mahlberg *et al.*, 2004; Mittino *et al.*, 2004; Freeman *et al.*, 2005; Gnanadesigan *et al.*, 2005; Kitson *et al.*, 2005; John *et al.*, 2007; Vizcaychipi *et al.*, 2007; Takeshita *et al.*, 2009; Marechal *et al.*, 2011; Peacock *et al.*, 2011; El-Okdi *et al.*, 2014; Falls *et al.*, 2014; Lamberg *et al.*, 2014; Shakoor *et al.*, 2014; UK_Medicines_information_pharmacists, 2014)
Fentanyl	-112.5 µg/h patch (2.7 mg) -25 µg/h patch (0.6 mg) -50-350 µg i.v. over a few hours -up to 200 µg i.v./h (48 mg)	(Turkel *et al.*, 2001; Roy *et al.*, 2003; Ailawadhi *et al.*, 2007; Ozkardesler *et al.*, 2008; Rang *et al.*, 2008; Guo *et al.*, 2009; Alkhatib *et al.*, 2010; Altman *et al.*, 2010; Kirschner *et al.*, 2010; Reich *et al.*, 2010; Rastogi *et al.*, 2011; Gollapudy *et al.*, 2012; Mugele *et al.*, 2012; Samartzis *et al.*, 2013; Gaffney *et al.*, 2015; Hillman *et al.*, 2015; Koury *et al.*, 2015; Larson *et al.*, 2015; Robles, 2015; Shah *et al.*, 2016)
Tapentadol	NR, fatal overdose	(Franco *et al.*, 2014)
Oxycodone	-50 mg p.o. 2/d (100) -5-10 mg p.o. 6/d (30-60) -20 mg p.o. 2/d (40) -40 mg p.o. 2/d (80)	(Rosebraugh *et al.*, 2001; Gnanadesigan *et al.*, 2005; Karunatilake *et al.*, 2006; Kirschner *et al.*, 2010; Reich *et al.*, 2010; Rastogi *et al.*, 2011; Gollapudy *et al.*, 2012; Walter *et al.*, 2012; Song, 2013; Falls *et al.*, 2014; Hillman *et al.*, 2015)
Methadone	-30 mg p.o. 3/d (90) -5 mg p.o. 2/d (10) -30 mg p.o. 4/d (120)	(Bush *et al.*, 2006; Rastogi *et al.*, 2011; Hillman *et al.*, 2015)
Dextro-methorphan	-15 mg d/d (45) -1440 mg overdose -overdose case -overdose case -960 mg overdose	(Nierenberg *et al.*, 1993; Skop *et al.*, 1994; Navarro *et al.*, 2006; Ganetsky *et al.*, 2007; Schwartz *et al.*, 2008; Szakaly *et al.*, 2008; Monte *et al.*, 2010; Kinoshita *et al.*, 2011; Tanaka *et al.*, 2011; Sethi *et al.*, 2012)
Pethidine	-230 mg/8h parenteral -25 mg i.v. single dose -30 mg i.v. single dose	(Dougherty *et al.*, 2002; Tissot, 2003; Altman *et al.*, 2007; Das *et al.*, 2008; Guo *et al.*, 2009)
Morphine	-NR[c] -10 mg p.o.4-6/d (40-60 mg) -30 mg[c]	(Stanford *et al.*, 1999; Kitson *et al.*, 2005; Vizcaychipi *et al.*, 2007; Mateo-Carrasco *et al.*, 2015)
Buprenorphine	NR, misuse	(Isenberg *et al.*, 2008)
Hydrocodone	-NR -5 mg p.o. 4/d (20)[b]	(Gnanadesigan *et al.*, 2005; Altman *et al.*, 2007)
Hydro-morphone	-50 mg i.v. 4/d (200)[b] -2 mg i.v. single dose[a]	(Altman *et al.*, 2007; Altman *et al.*, 2010)

[a]together with higher doses of fentanyl which were considered the main cause
[b]together with pethidin which was considered the main cause
NR, not reported
[c]together with tramadol

References for supplementary Table S1

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