International Journal of Neuropsychopharmacology (2018) 21(10): 926–931

doi:10.1093/ijnp/pyy047
Advance Access Publication: May 29, 2018
Brief Report

Brief report

Monoamine Transporter and Receptor Interaction Profiles in Vitro Predict Reported Human Doses of Novel Psychoactive Stimulants and Psychedelics

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Abstract

Background: Pharmacological profiles of new psychoactive substances can be established rapidly in vitro and provide information on potential psychoactive effects in humans. The present study investigated whether specific in vitro monoamine transporter and receptor interactions can predict effective psychoactive doses in humans.
Methods: We correlated previously assessed in vitro data of stimulants and psychedelics with human doses that are reported on the Internet and in books.
Results: For stimulants, dopamine and norepinephrine transporter inhibition potency was positively correlated with human doses, whereas serotonin transporter inhibition potency was inversely correlated with human doses. Serotonin 5-hydroxytryptamine-2A (5-HT_{2A}) and 5-HT_{2C} receptor affinity was significantly correlated with psychedelic doses, but 5-HT_{1A} receptor affinity and 5-HT_{2A} and 5-HT_{2B} receptor activation potency were not.
Conclusions: The rapid assessment of in vitro pharmacological profiles of new psychoactive substances can help to predict psychoactive doses and effects in humans and facilitate the appropriate scheduling of new psychoactive substances.

Keywords: new psychoactive substance, stimulants, psychedelics, receptor, transporter

Introduction

The unprecedented proliferation of new psychoactive substances (NPSs) over the last decade has introduced a variety of substance classes to recreational drug users worldwide. The Internet plays a major role in the distribution of such compounds and in acquiring information about their effects and reported subjective effective doses in substance users. From 2011 to 2017, we assessed the monoamine transporter and receptor interaction profiles of more than 100 NPSs and related classic amphetamine-type and psychedelic drugs of abuse using the same in vitro assays and procedures in our laboratory (Simmler et al., 2013; Simmler et al., 2014a, 2014b; Rickli et al., 2015a, 2015b, 2015c, 2016; Luethi et al., 2018a, 2018b, 2018c, 2018d). The compounds that we investigated can predominantly be classified as stimulants or psychedelics based on their pharmacological and reported psychoactive effect profiles. Stimulants exert their pharmacological effects mainly by interacting with transmembrane monoamine transporters (i.e., norepinephrine [NE], dopamine [DA], and serotonin [5-hydroxytryptamine (5-HT)] transporters [NET, DAT, and SERT, respectively]), either as inhibitors or as transporter substrates that mediate the non-exocytotic release of neurotransmitters (Rothman and Baumann, 2003). Psychedelics mediate their mind-altering effects by interacting with 5-HT receptors, mainly 5-HT_{2A} receptor agonism (Nichols, 2016; Liechti, 2017). The present study

Received: January 24, 2018; **Revised:** April 17, 2018; **Accepted:** May 24, 2018

investigated whether (1) in vitro monoamine transporter inhibition potencies and (2) in vitro serotonin receptor binding and activation can be used to predict human doses of stimulants and psychedelics, respectively, that are reported on online drug information websites and in books.

Methods

Drugs

The present study included drugs for which we previously investigated and published in vitro pharmacological profiles using identical assays and procedures in our laboratory (Simmler et al., 2013; Simmler et al., 2014a, 2014b; Rickli et al., 2015a, 2015b, 2015c, 2016; Luethi et al., 2018a, 2018b, 2018c, 2018d). These drugs could be categorized as either psychostimulants or psychedelics based on their chemical structure and reported pharmacological effects. Substances that predominantly inhibited monoamine transporters were classified as stimulants. Substances that most potently bound to 5-HT_2 receptors were pharmacologically classified as psychedelics. Five aminoindanes, 8 benzofurans, 28 cathinones, 3 piperazines, 10 piperidines, and 6 other NPSs were categorized as psychostimulants. One benzodifuran, 1 ergoline, and 7 tryptamines were categorized as psychedelics. The class of phenethylamines was further divided into 15 stimulant phenethylamines (amphetamine-type substances) and 36 psychedelic phenethylamines (ring-substituted phenethylamines, including 2C drugs and their methoxybenzyl [NBOMe] analogs). The stimulants are listed in supplementary Table 1. The psychedelics are listed in supplementary Table 2.

Dose Estimates

Dose estimates for human psychoactive doses were based on information that is found on the websites erowid.org, psychonautwiki.org, and tripsit.me (accessed December 17, 2017) and in published books and other publications (Shulgin and Shulgin, 1995, 1997; Simmler et al., 2013; Trachsel et al., 2013). The average midrange of the common dose range that is reported on the websites or in the books was taken as the dose estimate. Unless stated otherwise, oral doses of the racemic mixtures were used for this study.

Monoamine Transporter Inhibition

Norepinephrine, DA, and 5-HT uptake inhibition was assessed in human embryonic kidney 293 cells that were transfected with the human NET, DAT, or SERT as previously described in detail (Luethi et al., 2018c). Briefly, the cells were suspended in buffer and incubated with the drugs for 10 minutes before [^{3}H]-NE, [^{3}H]-DA, or [^{3}H]-5-HT at a final concentration of 5 nM was added for an additional 10 minutes to initiate uptake transport. The cells were then separated from the uptake buffer by centrifugation through silicone oil. The centrifugation tubes were frozen in liquid nitrogen, and the cell pellet was cut into scintillation vials that contained lysis buffer. Scintillation fluid was added, and uptake was quantified by liquid scintillation counting. Transporter inhibitors (10 μM nisoxetine for the NET, 10 μM mazindol for the DAT, and 10 μM fluoxetine for the SERT) were added to assess nonspecific monoamine uptake. Monoamine uptake data were fit by nonlinear regression to variable-slope sigmoidal dose-response curves, and IC_{50} values were determined using Prism 7.0a software (GraphPad).

5-HT Receptor Binding Affinities

Radioligand binding affinities for 5-HT receptors were assessed as previously described in detail (Luethi et al., 2018d). Briefly, membrane preparations overexpressing the respective human receptors were incubated for 30 minutes (5-HT_{1A} and 5-HT_{2A} receptors) or 2 hours (5-HT_{2C} receptor) with radiolabeled selective ligands at concentrations equal to K_d, and ligand displacement by the compounds was measured. Specific binding of the radioligand to the target receptor was defined as the difference between total binding and nonspecific binding that was determined in the presence of competitors. The following radioligands and competitors, respectively, were used: 1.39 nM [^{3}H]8-hydroxy-2-(di-*n*-propylamine)tetralin and 10 μM pindolol (5-HT_{1A} receptor), 0.45 nM [^{3}H]ketanserin and 10 μM spiperone (5-HT_{2A} receptor), and 1.6 nM [^{3}H]mesulgerine and 10 μM mianserin (5-HT_{2C} receptor).

Activity at the 5-HT_{2A} Receptor

Activity at the 5-HT_{2A} receptor was assessed as previously described in detail (Luethi et al., 2018a). Briefly, NIH-3T3 cells expressing the human 5-HT_{2A} receptor were incubated in buffer for 1 hour at 37°C before 100 μL of dye solution (fluorescence imaging plate reader [FLIPR] calcium 5 assay kit; Molecular Devices) was added to each well, and the plates were again incubated for 1 hour at 37°C. The plates were then placed in a FLIPR, and 25 μL of the test drugs that were diluted in buffer was added online. The increase in fluorescence was measured for 51 s. EC_{50} values were derived from the concentration-response curves using nonlinear regression.

Activity at the 5-HT_{2B} Receptor

Activity at the 5-HT_{2B} receptor was assessed as previously described in detail (Luethi et al., 2018a). Briefly, human embryonic kidney 293 cells that expressed the human 5-HT_{2B} receptor were incubated in growth medium overnight. The growth medium was then removed by snap inversion, and 100 μL of the calcium indicator Fluo-4 solution (Molecular Probes) was added to each well. The plates were incubated for 45 minutes at 31°C. The Fluo-4 solution was then removed by snap inversion, and 100 μL of Fluo-4 solution was added a second time for 45 minutes at 31°C. The cells were washed using an EMBLA cell washer, and 100 μL of assay buffer was added. The plates were then placed in a FLIPR, and 25 μL of the test substances that were diluted in buffer was added online. The increase in fluorescence was measured for 51 seconds. EC_{50} values were derived from the concentration-response curves using nonlinear regression.

Statistical Correlation

Mean estimated dose values were correlated with previously published mean IC_{50} values for the monoamine transporter inhibition of stimulants and the mean serotonin receptor affinity (K_i) and receptor activation (EC_{50}) values of psychedelics. The Spearman rank-order correlation coefficient (r_s) was computed using Prism 7.0a software (GraphPad). Values of $P < .05$ (2-tailed) were considered statistically significant. Multiple regression analysis was conducted to assess the relative contribution of different predictors to the dose estimate using Statistica 12 software (StatSoft) after logarithmic transformation of the data.

Results

Based on the reported information, dose estimates could be made for 54 of 75 stimulants and 35 of 45 psychedelics. The doses apply to the oral route of administration if not indicated otherwise (supplementary Tables 1 and 2). References for the information sources of the pharmacological data and for the dose estimates for each substance are listed in supplementary Tables 1 (stimulants) and 2 (psychedelics).

Stimulants

Correlations between transporter inhibition potencies (mean IC_{50} values) of stimulants and their mean dose estimates are shown in Figure 1. Inhibition potency values of the NET and DAT were significantly correlated with the human dose estimates (r_s=0.48, P<.001, n=54, and r_s=0.60, P<.001, n=54, respectively). Furthermore, the NET and DAT inhibition potencies were significantly intercorrelated (r_s=0.61, P<.001, n=74). In contrast, the inhibition potency values of the SERT were inversely correlated with the dose estimates (r_s=-0.41, P<.01, n=54) and inversely intercorrelated with DAT inhibition (r_s=0.26, P<.05, n=73) but not NET inhibition. When DAT and NET inhibition was used as the predictor within a multiple regression analysis to predict the dose, DAT inhibition and NET inhibition alone were significant predictors (R=0.55, P<.001, and R=0.51, P<.001, respectively) when entered alone, but adding NET to DAT inhibition only minimally and nonsignificantly increased the overall prediction (multiple R=0.59, P<.001). However, SERT inhibition was inversely correlated with dose when analyzed alone (R=0.36, P<.01) and relevantly and significantly increased the overall prediction when it was added to NET and DAT inhibition (multiple R=0.63, P<.001, n=54).

Psychedelics

Correlations between 5-HT receptor affinities (mean K_i values) and their dose estimates are shown in Figure 2. Reported human doses for psychedelics were significantly correlated with 5-HT_{2A} and 5-HT_{2C} receptor binding (r_s=0.62, P<.001, n=35, and r_s=0.69, P<.001, n=35, respectively) but not with 5-HT_{1A} receptor binding (r_s=-0.18, P=.3, n=35). The 5-HT_{2A} and 5-HT_{2C} affinity values were significantly intercorrelated (r_s=0.90, P<.001, n=45), and the 5-HT_{1A} and 5-HT_{2A} affinity values were inversely intercorrelated (-0.32, P<.05, n=45). No correlation was found between 5-HT_{1A} receptor binding and 5-HT_{2c} receptor binding.

5-HT_{2A} receptor activation potencies (mean EC_{50} values) did not correlate with reported human doses (r_s=-0.08, P=.6, n=35). Four substances did not activate the 5-HT_{2B} receptor in the investigated concentration range, and these substances thus could not be included in the statistical analysis. The 5-HT_{2B} receptor activation of the remaining psychedelics did not correlate with the dose estimates (r_s=0.25, P=.2, n=31).

Discussion

Stimulants

In the present study, we found that both NET and DAT inhibition potencies were correlated highly significantly with human doses that are reportedly used across a larger set of psychoactive, mostly amphetamine-type stimulants. In contrast, SERT inhibition potency was inversely correlated with human doses, a finding that is consistent with the notion that serotonergic

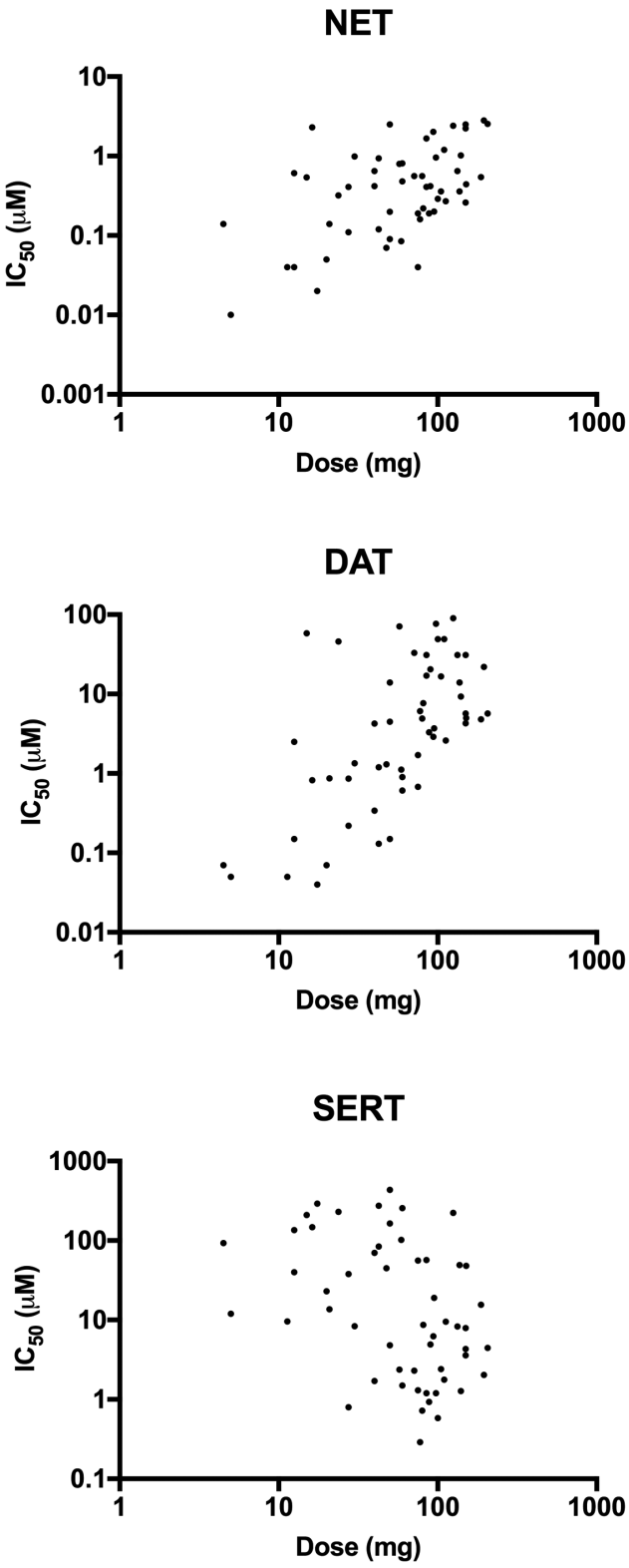

Figure 1. Correlations between dose estimates of stimulants and their transporter inhibition potencies (mean IC_{50} values).

activity is inversely linked to the drug abuse liability of amphetamine-type substances (Ritz et al., 1987; Kuhar et al., 1991; Wee et al., 2005; Wee and Woolverton, 2006). We also found a significant intercorrelation between NET and DAT inhibition potencies

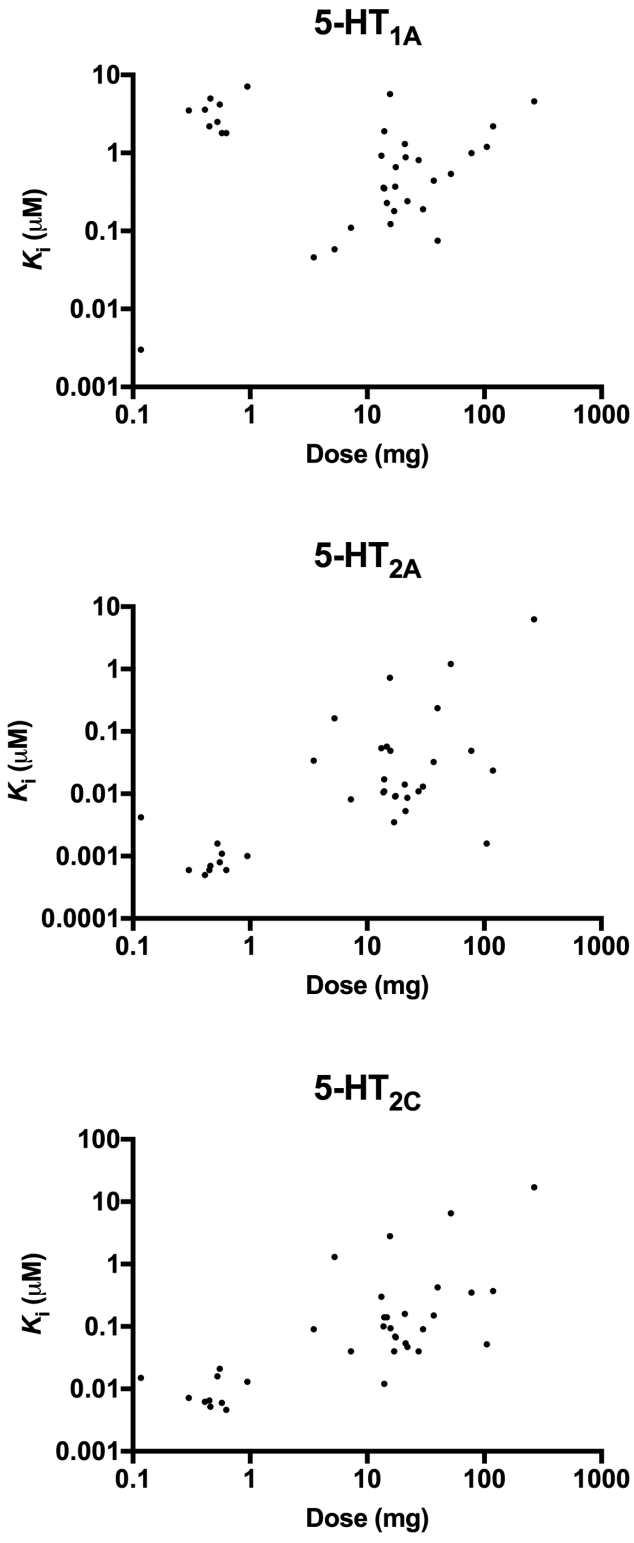

Figure 2. Correlations between dose estimates of psychedelics and their serotonin 5-HT receptor affinities (mean K_i values).

across substances, which is unsurprising given their similarity (i.e., high amino acid sequence similarity [Andersen et al., 2015]) and the ability of both transporters to transport NE and DA across the cell membrane (Gu et al., 1994). The present data are consistent with a small previous study that reported that oral doses of 5 classic amphetamine-type stimulants used in clinical studies correlated with their NE-releasing potencies, although no significant correlation was shown for DA release (Rothman et al., 2001). In another study, Iversen and colleagues found no correlation between uptake inhibition potency and doses of stimulant drugs producing subjective effects (Iversen et al., 2013). The lack of correlation may relate to the small number of compounds tested.

We previously showed that DAT and NET inhibition potency but not SERT inhibition potency (IC_{50} values) were correlated with psychotropic effective doses within a subset of substances that were also included in the present analysis (Simmler et al., 2013). Altogether, the present study showed that DAT and NET inhibition potency values that are defined in vitro can be used to estimate whether a novel substance is psychoactive in humans, and the dose can be predicted when other known substances are co-analyzed as references. This finding has important implications because it indicates that relatively fast and simple in vitro measures are useful for legally scheduling novel substances as psychoactive and thus as illegal NPSs. Both the DAT and NET may serve as predictors of the human dose, whereas SERT inhibition potency can be used as an additional indicator, predicting lower clinical potency of the substance. Furthermore, the DAT/SERT inhibition ratio, which is defined as 1/DAT IC_{50}: 1/SERT IC_{50} (Baumann et al., 2012), is a marker of the reinforcing effects and abuse liability of a substance (Baumann et al., 2000). Compounds with higher SERT vs DAT inhibition potency are typically associated with 3,4-methylenedioxymethamphetamine-like entactogenic effects, whereas drugs with high DAT vs SERT inhibition potency exert amphetamine-type psychostimulant effects and pose a higher risk for addiction (Simmler et al., 2013, 2014a; Liechti, 2014; Suyama et al., 2016).

Psychedelics

We showed that the doses of psychedelics were correlated with 5-HT_{2A} receptor affinity (K_i values) but not with receptor activation potency in the calcium release assay used to determine EC_{50} values. 5-HT_{2A} receptor activation is assumed to mediate the mind-altering effects of psychedelics (Glennon et al., 1984; Titeler et al., 1988) and such effects can be blocked by 5-HT_{2A} receptor antagonists, such as ketanserin (Preller et al., 2017). All of the psychedelics that were included in our study were receptor agonists, and the correlation with receptor binding but not activation might be explained by higher sensitivity of the ligand-binding assays compared with the receptor activation assay. There are different 5-HT_{2A} receptor activation assays, and the potencies for inducing calcium release in the assay that was used in the present study may not reflect the same pathway or mechanism that mediates the subjective effects of hallucinogens in humans. In fact, others have also reported that high-affinity agonist binding did not correlate well with the receptor activation of 5-HT_2 receptors (Roth et al., 1997; Acuña-Castillo et al., 2002). Despite the lack of utility for predicting doses, the determination of 5-HT_{2A} receptor activity remains crucial for determining whether a NPS has receptor agonist properties and may thus be classified as a psychedelic or whether it is an antagonist that only binds to the receptor. The present study showed that 5-HT_{2A} receptor binding allows an estimate of the dose at which the substance is psychoactive in humans. Besides the correlation of the dose estimates for psychedelics with 5-HT_{2A} receptor affinities, we also found a correlation with 5-HT_{2C} receptor affinities. Today, it is widely accepted that 5-HT_{2A} receptor activation is crucial for the action of psychedelics (Preller et al., 2017); the

role of 5-HT_{2C} receptor activation, however, remains enigmatic. As all known psychedelics are both 5-HT_{2A} and 5-HT_{2C} agonists, a contribution of 5-HT_{2C} activation to psychedelic effects cannot be excluded (reviewed in Nichols, 2004, 2016).

Limitations

The outcomes of the present analysis highly depended on the types of substances that were included and may be different for other sets of psychoactive compounds. Although valid pharmacological data were used, the dose estimates were mainly derived from user reports. No controlled studies are currently available for most NPSs, but doses for some of the substances included in the present analysis are available from clinical studies. These doses were comparable to the reported recreational doses. Doses derived from clinical studies are available for mephedrone (200 mg; Papaseit et al., 2016), 3,4-methylenedioxymethamphetamine (100–125 mg; Tancer and Johanson, 2003; Papaseit et al., 2016; Vizeli and Liechti, 2017); MDAI (3 mg/kg; V. Auwärter et al., personal communication); cathinone (0.5 base mg/kg; Brenneisen et al., 1990); 4-fluoroamphetamine (100 mg; K. Kuypers et al., personal communication); D-amphetamine (15–40 mg; Martin et al., 1971; Brauer and de Wit, 1996; Dolder et al., 2017b); methamphetamine (15–30 mg; Martin et al., 1971; Gouzoulis-Mayfrank et al., 1999); MDEA (2 mg/kg; Gouzoulis-Mayfrank et al., 1999); BZP (100 mg; Lin et al., 2011); mCPP (0.5–0.75 mg/kg; Tancer and Johanson, 2003); methylphenidate (40–60 mg; Schmid et al., 2014); cocaine (48–96 mg; Volkow et al., 2000); diclofensine (50 mg; Funke et al., 1986); LSD (0.1 mg; Dolder et al., 2017a); 2C-B (20 mg; Gonzalez et al., 2015); mescaline sulfate (500 mg; Hermle et al., 1992); and psilocin/psilocybin (5–20 mg; Studerus et al., 2012). Therefore, even though the dose estimates of the current study were not derived from clinical studies, they are in accordance with the available clinical data.

Not accounted for in the in vitro assays were in vivo factors (e.g., bioavailability, route of administration, distribution, and brain penetration), which may influence clinical potency.

Conclusion

The present study found that in vitro pharmacological profiles of substances that interact with monoaminergic systems allow the characterization of substances as stimulants or psychedelics and may be used to predict human psychoactive doses. For stimulants, potent DAT and NET inhibition was associated with lower pharmacological doses in humans. In contrast, higher SERT inhibition potency was an additional indicator of lower stimulant potency and higher human doses. The potency of psychedelics was best predicted by 5-HT_{2A} and 5-HT_{2C} binding affinity. In contrast, the calcium mobilization assay used to determine 5-HT_{2A} receptor activation potency did not predict the clinical potency of psychedelics. However, it is a necessity to determine whether a drug is a 5-HT_{2A} agonist and therefore likely a psychedelic in humans.

Funding

This work was supported by the Federal Office of Public Health (grant no. 16.921318).

Acknowledgments

The authors thank Michael Arends for text editing.

Statement of Interest

None.

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