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Estimating effects of new psychoactive substances (NPS) based on in vitro neurotoxicity data

The use of new psychoactive substances (NPS) is increasing and currently > 600 NPS have been reported. However, limited information on neuropharmacological and toxicological effects of NPS is available, hampering risk characterization.

We reviewed the literature on the *in vitro* neuronal modes of action to obtain effect fingerprints of different classes of illicit drugs and NPS. The most frequently reported NPS were selected for review: cathinones (MDPV, α-PVP, mephedrone, 4-MEC, pentedrone, methylone), cannabinoids (JWH-018), (hallucinogenic) phenethylamines (4-fluoroamphetamine, benzofurans (5-APB, 6-APB), 2C-B, NBOMes (25B-NBOMe, 25C-NBOMe, 25I-NBOMe)), arylcyclohexylamines (methoxetamine) and piperazine derivatives (mCCP, TFMPP, BZP).

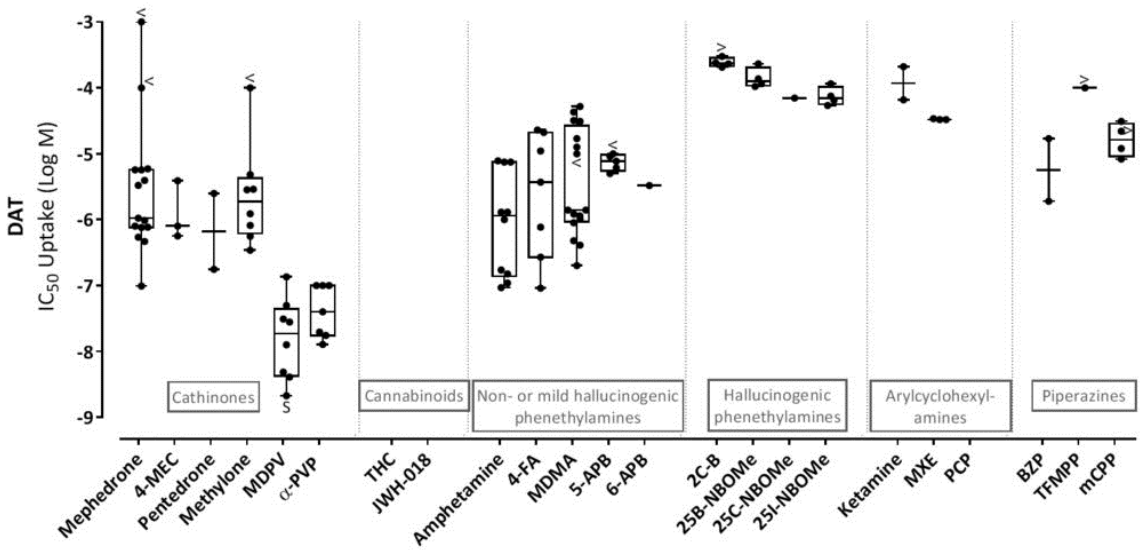


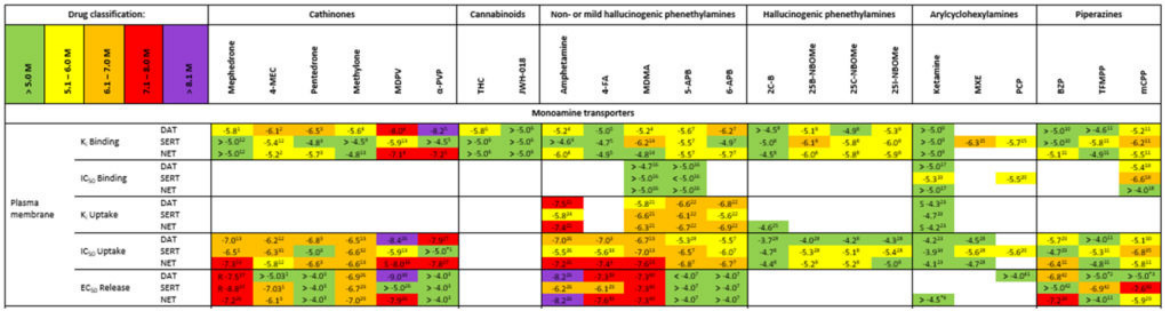
Fig. 1. Inhibition of the dopamine reuptake transporter by different classes of drugs.

Not surprisingly, effects on plasma membrane monoamine reuptake transporters are well studied for most illicit drugs and NPS (Fig. 1). Binding profiles for receptors other than dopamine and serotonin or ion channels are largely absent, with the exception of CB receptors for (synthetic) cannabinoids. Similarly, functional data regarding effects on receptors, ion channels and integrated endpoints such as neuronal activity are largely missing. Whether these data gaps are simply due to a lack of data (i.e. not studied) or result from publication bias, which likely hampers publication of negative/low potency results, is unknown.

Furthermore, the available data clearly argue for additional measurements as the data show a large variation in reported effects and effect sizes, often spanning up to 4-5 orders of magnitude. In addition, for many NPS-target combinations only a single data point is available. Also, for many targets, only binding data is available

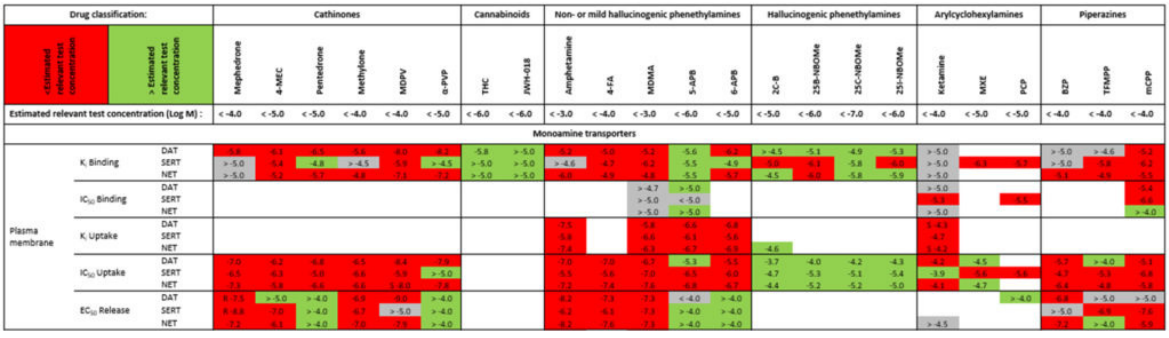
and functional data is lacking. Similarly, not all studies report the maximum effect, although EC_{50} values are reported.

Nevertheless, the data clearly highlight the main mechanisms of action for the different NPS studied (Tab. 1), *i.e.* inhibition and/or reversal of monoamine reuptake transporters (cathinones and non-hallucinogenic phenethylamines), activation of 5-HT_2 receptors (hallucinogenic phenethylamines and piperazines), activation of cannabinoid receptors (cannabinoids) and inhibition of NDMA receptors (arylcyclohexylamines).



Tab. 1. (Part of) Effect fingerprint of monoamine reuptake by NPS and other drugs. The lowest reported drug concentration (log M) that affects the target is listed. The colors represent the potency of a drug to affect a specific target.

Importantly, we identified additional targets by relating reported effect concentrations to the estimated human brain concentrations during recreational use (Tab. 2). These additional targets include dopamine, α- and β-adrenergic, $GABA_A$ and acetylcholine receptors, which may all contribute to the observed clinical symptoms following exposure. While the effect fingerprints of NPS are still incomplete, relating them to human relevant concentrations highlights that many targets can contribute to the clinical symptoms.



Tab. 2. (Part of) Effect fingerprint of monoamine reuptake by NPS and other drugs related to estimated human brain concentrations. Reported effect concentrations are color-labeled if above (green) or within (red) the relevant test concentration (second row).

To obtain (more) useful neuropharmacological effect fingerprints, a battery of *in vitro* assays should be applied that preferably focusses on functional effects rather than on binding. Based on our review of affected targets, such a battery should include at least: inhibition and reversal of both plasma membrane and vesicular

monoamine transporter as well as activation or inhibition of dopamine, serotonin, ACh, GABA, glutamate, cannabinoid, and adrenergic receptors. Notably, investigating the effect of a specific NPS on an integrated endpoint, such as neuronal activity, could replace several single targets in the future.

These fingerprints can be implemented in the risk assessments of NPS that are necessary for eventual control measures to reduce Public Health risks.

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Publication

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