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ORIGINAL INVESTIGATION

Linking the pharmacological content of ecstasy tablets to the subjective experiences of drug users

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Abstract
Rationale Most studies on the subjective effects of ecstasy are based on the assumption that the substance that was taken is 3,4-methylenedioxymethamphetamine (MDMA). However, many tablets sold as ecstasy contain other substances and MDMA in varying doses. So far, few attempts have been made to take this into account while assessing subjective effects.
Objectives This study aims to link the pharmacological content of tablets sold as ecstasy to the subjective experiences reported by ecstasy users.
Methods Self-reported effects on ecstasy tablets were available from 5,786 drug users who handed in their tablets for chemical analysis at the Drug Information and Monitoring System (DIMS) in the Netherlands. Logistic regression was employed to link the pharmacological content of ecstasy tablets to the self-reported subjective effects and compare effects with MDMA to other substances present.
Results MDMA showed a strong association with desirable subjective effects, unparalleled by any other psychoactive substance. However, the association of MDMA was dose-dependent, with higher doses (>120 mg/tablet) likely to evoke more adverse effects. The novel psychostimulants mephedrone and *p*-fluoroamphetamine were considered relatively desirable, whereas *meta*-chlorophenylpiperazine (mCPP) and *p*-methoxymethamphetamine (PMMA) were strongly associated with adverse subjective effects. Also, 3,4-methylene-dioxyamphetamine (MDA) and benzylpiperazine (BZP) were not appreciated as replacement for MDMA.
Conclusion Linking the pharmacological content of ecstasy sold on the street to subjective experiences contributes to a better understanding of the wide range of subjective effects ascribed to ecstasy and provides a strong rationale for the prolonged endurance of MDMA as the key ingredient of the ecstasy market.

Keywords 3,4-Methylenedioxymethamphetamine (MDMA) · Ecstasy · Subjective effects · Desirable · Adverse · Dose

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Introduction

There has been an accumulation of data on the (acute) subjective effects of ecstasy (Verheyden et al. 2002; Huxster et al. 2006; Baylen and Rosenberg 2006; Sumnall et al. 2006) ranging from desirable to adverse experiences (Peroutka et al. 1988; Liechti et al. 2001; Baylen and Rosenberg 2006; Sumnall et al. 2006). Predictors for acute subjective effects of ecstasy include setting, precautions that were taken, pattern of use and dose (Parrott et al. 2002; Thomasius et al. 2003; Parrott 2006; Parrott et al. 2006; Kolbrich et al. 2008). In addition, gender may influence the subjective effects of ecstasy with more profound hallucinogen-like effects in women (Liechti et al. 2001). Finally, changes over time were reported in long-term

ecstasy users with a general decline of positive subjective effects and rather stable levels of negative experiences (Murphy et al. 2006). In contrast to these psychobiological and environmental predictors of the subjective effects of ecstasy, very little is known about the relationship between the pharmacological composition of ecstasy tablets and subjective effects.

The term ecstasy generally refers to 3,4-methylenedioxymethamphetamine (MDMA) and its structural analogues 3,4-methylene-dioxyethylamphetamine (MDEA), 3,4-methylene-dioxyamphetamine (MDA) and 2-methylamino-1-(3,4-methylenedioxyphenyl)butane (MBDB) (Schifano et al. 2006). These analogue substances mostly seem to exert similar subjective effects as MDMA (Hegadoren et al. 1999). Whereas MDMA is the main component, other psychoactive substances were also frequently encountered in tablets sold as ecstasy (Cole et al. 2002; Simonsen et al. 2003; Camilleri and Caldicott 2005; Kenyon et al. 2005; Tanner-Smith 2006; Vogels et al. 2009). Mostly, these substances are similar to MDMA in structure or effect, but entirely other classes of pharmacological compounds were also marketed through ecstasy tablets (Boyer et al. 2001; Camilleri and Caldicott 2005; Bossong et al. 2010; Brunt et al. 2010). Also, the dose of MDMA may vary considerably between different batches of tablets (Vogels et al. 2009).

Whereas the ecstasy market in the EU has been relatively stable during the first decade of the 21st century with ecstasy tablets mainly containing MDMA and/or MDMA-like substances (Simonsen et al. 2003; Parrott 2004; Giraudon and Bello 2007; Vogels et al. 2009), a sharp drop in MDMA and MDMA-like substances has been noted in recent years all across the EU (Brunt et al. 2010; EMCDDA 2010; Schifano et al. 2011), a situation known outside the EU already for a much longer period (UNODC 2010). Secondly, novel compounds, referred to as designer drugs, were introduced via the ecstasy market throughout the years, e.g., piperazine derivates acting on the serotonin system in an effort to mimic MDMA actions (de Boer et al. 2001; Staack and Maurer 2003; Staack 2007; Bossong et al. 2010).

The pharmacological composition of ecstasy tablets is obviously of crucial importance for the perceived subjective effects by drug users. The discrepancy between tablets sold as "ecstasy" and the actual content has been addressed before emphasizing the importance of a better insight into the market of illicit drugs when discussing subjective effects reported by drug users (Parrott 2004; Tanner-Smith 2006). Conclusions about subjective effects could be misleading if ecstasy tablets turn out to be of varying purity or contain unsuspected pharmacological compounds. For instance, piperazine derivates have been on the ecstasy market for more than 10 years now and the different piperazines are chemically heterogeneous, which is reflected in different pharmacokinetics and subjective effects. Some studies have reported similar subjective effects of various piperazine derivatives and MDMA (Tancer and Johanson 2003; Lin et al. 2011), whereas other studies have indicated substantial differences in the subjective effects of these designer compounds and MDMA (Bossong et al. 2010; Jan et al. 2010). Similar differences in subjective effects were found for other pharmacological classes of compounds commonly found in ecstasy tablets (Aerts et al. 2000; Brunt et al. 2010).

Overall, relatively little is known about the link between the pharmacological composition of ecstasy tablets, sold on the street, and the effects experienced by drug users. This study aims to describe the relationship between the psychoactive content in ecstasy tablets and self-reported effects of its users. To this aim, subjective effects linked to chemically analyzed ecstasy tablets were collected in retrospect from the database of the Drug Information and Monitoring System (DIMS) in the Netherlands and the relationship of the pharmacological content with these effects was studied.

Materials and methods

Participants

Participants were drug users that utilized the drug testing facilities of the DIMS. The DIMS covers all provinces and major cities in The Netherlands. Drug users handed in their drugs voluntarily and anonymously at a testing facility to have the pharmacological composition of their ecstasy tablets chemically analysed in order to know the possible health risks associated with their purchases. Tablets were tested by the laboratory and within 1 week prevention workers communicated the results to the individual drug users. For this study, only requests about tablets that were sold as ecstasy were included. Between 2000 and 2010, a total of 27,492 subjects asked for a chemical analysis of their ecstasy tablets. Of these, 5,786 (21%) also reported on previous subjective effects with the ecstasy tablet they handed in for analysis. In compliance with the DIMS guidelines, participants were treated anonymously and, therefore, no additional individual information was available.

Subjective effects

The testing facilities of the DIMS have direct personal contact with the drug users at the moment they hand in their drugs for laboratory analysis. If they had purchased several tablets from one batch and had already taken one, they were invited to report on their previous

subjective experiences with this tablet. Results of the chemical analyses were only available 1 week later and, therefore, the reported effects could not be biased by the analytical results. The section for reporting effects provided an open space to specify the details of the effects, like the specific psychological and physical effects. Regardless of the nature of the reported effects (physical or psychological), all effects were treated as subjective, as they were not measured otherwise. These items were not preselected by DIMS, and drug users were free in the choice of their own vocabulary in describing subjective effects. To facilitate further analysis, researchers of the DIMS (blind to the pharmacological composition of the tablet that was handed in and subsequently analysed) interpreted and recoded these reported effects into discrete terms used in scientific literature, because of the drug user's unfamiliarity with these (scientific) terms. In a final step, these discrete terms were classified into three main categories: (1) desirable effects, (2) adverse effects, and (3) lack of effects (see Table 1). For statistical purposes, it was decided to discriminate between desirable and adverse effects for further analyses, by comparing category 1 (desirable) to the combination of categories 2 and 3 (adverse and lack of effect) and similarly comparing category 2 (adverse) to the combination of categories 1 and 3 (desirable and lack of effect).

Pharmacological categorization

Categories of pharmacological contents were constructed, starting with the most potent psychoactive ingredients present in tablets in a substantial amount. Traces of pharmacological substances or additives with no pharmacological properties were disregarded for the categorization. Caffeine was not subcategorized, unless it was the only psychoactive compound present. Since a number of tablets consisted of more than one psychoactive component, a subcategorization was made of the combinations of the different psychoactive substances in the ecstasy tablets. All 5,786 tablets were categorized this way resulting in 22 mutually exclusive categories (see Table 2).

Drug analysis

Qualitative and quantitative chemical analyses of the drugs samples were performed using a set of analytical methods to identify known and unknown components. In principle, three different analytical procedures were used. As a first step, thin layer chromatography (TLC; Toxilab®A) was performed for identification. The analytes were identified by relating their position (RF) and color to standards through four stages of detection: a coloring stage I (Marquis reagent), a washing stage II, an UV fluorescence stage III, and finally a coloring stage IV with Dragendorff's reagents. An extensive library enabled to locate known spots and the possible crude identification of new substances. As a second step, the quantification of the common components (e.g., amphetamine, methamphetamine, MDMA, MDA, MDEA, caffeine, cocaine, 2,5-dimethoxy-4-bromophenethylamine [2 C-B], *meta*-chlorophenylpiperazine [mCPP] and heroin) was performed with gas chromatography-nitrogen–phosphorous detection (GC-NPD) using an internal standard (Chirald, Sigma-Aldrich, Zwijndrecht, The Netherlands). Finally, gas chromatography–mass spectrometry (GC-MS) was used as a decisive instrument in cases where TLC and GC-NPD results were not in agreement with each other. This was necessary in approximately 10% of the samples. Also, GC-MS was used for the identification of unknown compounds or the quantification of

Table 1 The various subjective effects after ecstasy use as reported by the drug users at the drug testing facilities of the DIMS

Effect categories			
Desirable effect *N*=3,440 (59.5%)		Undesirable effect *N*=2,346 (40.5%)	
		Adverse effect *N*=924 (16.0%)	No effect *N*=1,422 (24.5%)
Liking, general	1,582	Nausea[a]	
Euphoric	752	Headache	453
Relaxed	688	Hallucinations	120
Arousal	789	Agitation	110
Sociable/entactogenic	529	Palpitations[a]	74
		Abdominal cramps	65
		Hyperthermic	40
		Seizure	26
		Dizziness	96
		Allergic reactions	44

Sometimes more than one subjective effect was mentioned

[a]Emergency treatments or hospitalizations were mentioned with these adverse effects

Table 2 Pharmacological categories in ecstasy tablets

Pharmacological categories	Prevalence		Average dose (±SD), mg/tablet	Min − max, mg/tablet
	N	%		
Total	5,786	100	–	–
One psychoactive substance only	5,343	92.3		
MDMA	4,044	69.9	82.5 (35.2)	2.0–218.0
mCPP	614	10.6	26.6 (13.8)	1.0–88.0
mCPP+metoclopramide[a]	126	2.2	33.1 (12.9)	2.0–55.0
MDA	107	1.8	44.2 (18.0)	3.0–104.0
BZP[a]	95	1.6	–	–
amphetamine	88	1.5	8.8 (7.7)	1.0–41.0
Mephedrone[a]	85	1.5	–	–
2 C-B	74	1.3	7.2 (3.2)	1.0–16.0
Caffeine	42	0.7	66.5 (55.0)	10.0–234.0
p-Fluoroamphetamine[a]	35	0.6	–	–
MDEA	33	0.6	60.9 (21.6)	5.0–124.0
Combinations of psychoactive substances	443	7.7		
MDMA+MDEA	146	2.5	66.8 (26.9)	6.0–174.0
MDMA+mCPP	114	2.0	50.1 (21.3)	2.5–95.3
MDMA+PMMA[a]	70	1.2	43.9 (31.1)	5.0–128.0
MDMA+amphetamine	65	1.1	67.3 (33.6)	6.0–166.0
MDMA+MDA	39	0.7	56.8 (23.7)	12.0–106.0
MDMA+2 C-B	2	<0.1	43.8 (6.5)	39.2–48.4
MDA+amphetamine	2	<0.1	–	–
MDA+MDEA	2	<0.1	–	–
BZP[a]+amphetamine	1	<0.1	–	–
BZP[a]+mCPP	1	<0.1	–	–
MDMA+MDA+MDEA	1	<0.1	–	–

Average dose MDMA is given in case of a combination with MDMA, average of mCPP is given in case of its combination with metoclopramide

[a]Dichotomous variables, not quantified by gas chromatography

uncommon compounds. All analyses were done in a Good Laboratory Practice (GLP)-compliant laboratory. The combination of various analytical methods has led to a comprehensive list of identified components in ecstasy tablets over the years.

Statistical analysis

Summary statistics (e.g., percentages) were used to describe the prevalence of subjective effects and pharmacological categories in the ecstasy tablets. Associations of pharmacological categories other than MDMA with subjective effects were obtained by multiple logistic regression. Pharmacological category, a categorical predictor with k categories was entered as $k-1$ dummy variables with MDMA as the reference category. This means that the regression coefficient b_j of the jth dummy variable reflects the effect of substance j relative to MDMA. Dose effects could not be taken into account for these analyses, because most of these other substances are not dosage-equivalent with MDMA. In all statistical analyses, effect estimates are presented as odds ratios (OR) relative to MDMA and the probabilities of the occurrence of an effect, given the value of the dummy variable x_j is estimated by:

$$P(\text{effect} \mid \text{subst} = j) = 1/(1 + \mathrm{e}^{-(b_0+b_j)})$$

where $P(\text{effect} \mid \text{substance} = j)$ denotes the probability of the effect for substance j and b_0 and b_j are estimates from the multiple logistic regression analysis.

For the dose–effect analysis of MDMA, dose was categorized in classes of 20 mg because the effect of dose on outcome was not linear in the logit (Hosmer and Lemeshow 2000). In the analyses of combinations of MDMA with other psychoactive substances, interactions between all combinations were found by logistic regression, so the dose effect of MDMA was left out of these analyses. All analyses were conducted separately for desirable effect vs. undesirable effect and adverse effect vs. desirable/no effect as dependent variable. For all analyses SPSS (version 17.0) software was used. Results were considered significant if $p<0.05$.

Results

Description of subjective effects

The various subjective effects that were described by the drug users were clustered as adjectives under three main subjective effect categories (see Table 1). Of the 5,786 drug users who reported a previous experience with an analysed ecstasy tablet, 59.5% reported desirable subjective effects, and 40.5% experienced undesirable effects, being either adverse (16.0%) or a lack of effect (24.5%). The subjective adverse effects category was richest in adjectives, ranging from agitation to palpitations. A total of 53 drug users (0.9%) reported emergency care treatment or even hospitalization due to the reported adverse effects, mostly nausea or hyperthermic seizures.

Description of pharmacological categories

Subdividing the content into categories led to 22 distinct pharmacological categories of ecstasy tablets (Table 2). MDMA alone was by far the most prevalent category (69.9%), followed by mCPP alone (10.6%) and all the other categories were pretty much spread out over the rest of the tablets. Caffeine was not included in the categories, unless tablets contained this substance exclusively (0.7%). Average dose per tablet for each of the pharmacological categories was calculated, except for pharmacological substances that were not quantified by the laboratory. In the case of a combination of MDMA with another psychoactive substance, only the average dose of MDMA (in mg/tablet) is given.

Distribution subjective effects

The vast majority (900/924 or 97.4%) of adverse subjective effects occurred in nine of the 22 pharmacological categories covering 15.6% of all the tablets, these categories were: mCPP, MDMA, MDMA+mCPP, MDA, MDMA +*p*-methoxymethamphetamine (PMMA), amphetamine, benzylpiperazine (BZP), mCPP+metoclopramide and 2 C-B (Fig. 1). To give an impression of the adverse subjective effects that were associated with which specific (combinations of) pharmacologic substances, the numbers and relative occurrences within the adverse effects category mentioned are presented for these nine pharmacological categories (Fig. 1). The remaining adverse effects were distributed in low occurrences amongst 11 other pharmacological categories: *p*-fluoroamphetamine (6), mephedrone (4), caffeine (4), MDMA+amphetamine (4), MDMA+MDA (2), MDA+amphetamine (1), mCPP+BZP (1), BZP+amphetamine (1), MDMA+MDEA+MDA (1), MDMA+2 C-B (1), and MDEA (1). With two of the pharmacological categories no adverse effects were reported (MDMA+MDEA and MDA+MDEA). MCPP alone (N=614) and its combination with MDMA (N=114) accounted for most cases with nausea (287/453 or 63.3%), whereas agitation and palpitations occurred more frequent with amphetamine and with MDA. The combination MDMA and PMMA (N=70) led to several reported cases of hyperthermic seizure in drug users.

Desirable effects, on the other hand, were mostly aspecific, such as general liking of the effect or relaxed feelings. The majority of desirable effects (3,102/3,440 or 90.2%) were reported across two pharmacological categories: MDMA (N=3,000) and MDMA+MDEA (N=102). General liking (38%), euphoria (21%) and sociability/entactogenic feelings (16%) were the most prevalent effects with MDMA alone. MDA (N=26), MDMA+MDA (N=26) and MDMA+mCPP (N=29) relatively caused more arousal and less sociability/entactogenic feelings (on average less than 12% of desirable effects) than MDMA or MDMA+MDEA, whereas MDMA +amphetamine (N=32) and MDEA (N=21) relatively caused more euphoria (both more than 40% of desirable effects). Increased sociability and entactogenic feelings, typically subscribed to ecstasy, was also reported with mephedrone (N=54) and *p*-fluoroamphetamine (N=17) (both more than 30% of desirable effects).

Linking pharmacological contents to subjective effects: statistical analysis

Dose–effect relationship of MDMA

The category MDMA alone consisted out of 4,044 tablets of varying doses. Logistic regression showed an interesting biphasic relationship between MDMA dose with subjective effects: MDMA dose was both positively related to desirable effects (OR, 1.012; 95% CI, 1.009–1.014; $p<0.001$) and adverse effects (OR, 1.024; 95% CI, 1.020–1.027; $p<0.001$). A more detailed analysis of the dose–effect relationship showed that these relationships were not linear in the logit. Entering dose as categorical variable, after categorising dosage into 20 mg categories, resulted in a more valid description of the dose response relationship as presented in Fig. 2. The curve for desirable effects shows that the probability of experiencing desirable effects increases until 81–100 mg MDMA, then it slowly decreases with high doses of MDMA showing increasingly lower probabilities of experiencing desirable effects. In contrast, the probability of experiencing adverse effects increases rapidly with MDMA doses exceeding 120 mg.

Other pharmacological contents and subjective effects

Differences in subjective effects between different ecstasy tablets containing only one psychoactive substance were

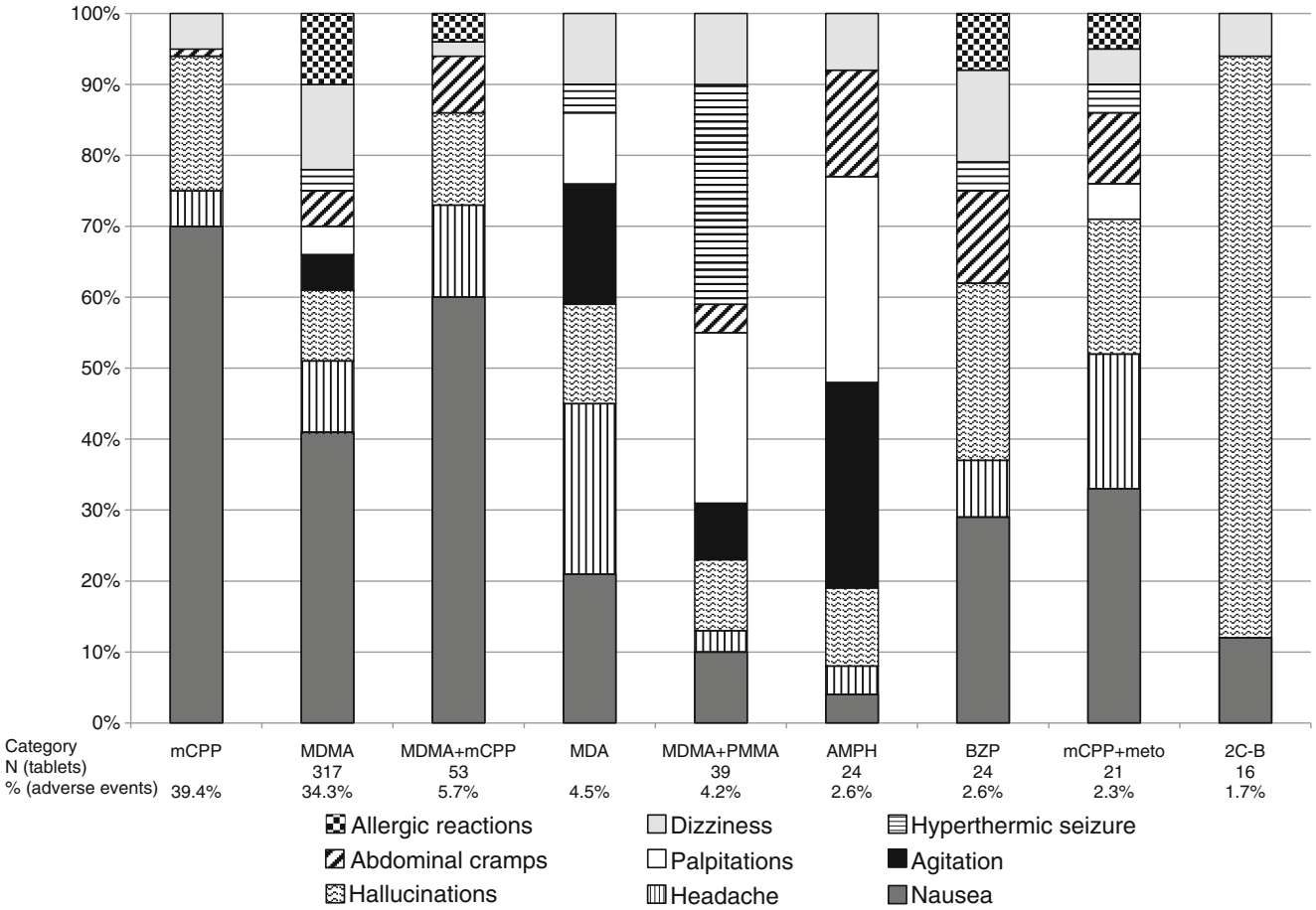


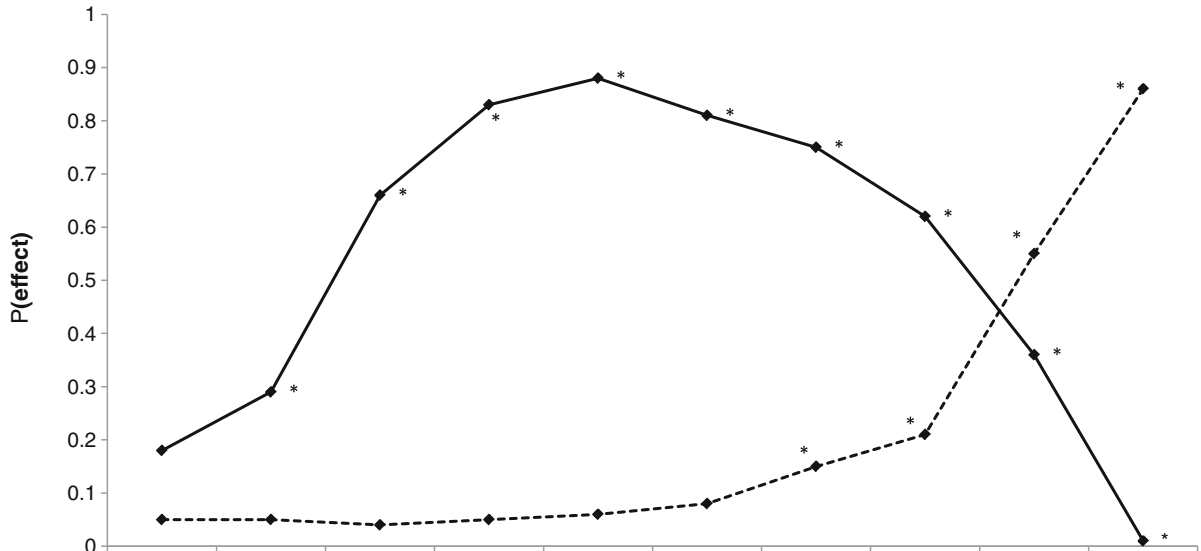
Fig. 1 Distribution of majority of adverse effects among nine different pharmacological categories. Amount of tablets is given and percentage of total within the adverse effects category; *AMPH* amphetamine, *meto* metoclopramide

analysed by multiple logistic regression, with MDMA alone as reference category (Table 3). Firstly, there is no single psychoactive substance that paralleled the desirable effects of MDMA. The probabilities were all lower than with MDMA alone (0.74) and in seven of ten categories, other than MDMA, the OR's were significantly lower than 1. Only MDEA, mephedrone and *p*-fluoroamphetamine were comparable to MDMA. Moreover, seven out of ten categories, other than MDMA, showed a higher probability of adverse effects compared to MDMA (Table 3). This was confirmed by the OR's for these categories, with especially mCPP and MDA showing robust increased likelihoods of experiencing adverse affects. In addition, BZP, amphetamine and 2 C-B were associated with more unpleasantness. Interestingly, if mCPP was combined with the psychoinactive anti-emetic compound metoclopramide, the likelihood of adverse subjective effects of mCPP almost disappeared. It should be noted, however, that this combination still had a relatively low probability of desirable effects.

If combinations of MDMA with one additional psychoactive substance were compared to MDMA alone, none of these combinations paralleled the probability of desirable effects of MDMA alone (Table 4). Together with the odds for desirable effects, the combinations of MDMA and its structural analogues (MDEA or MDA) were most comparable to MDMA alone. All other combinations had OR's considerably lower than 1. If adverse effects were taken into account, the contrast between MDMA and these combinations became even more pronounced, with MDMA in combination with PMMA or mCPP showing a very high likelihood of experiencing adverse affects (Table 4). On the other hand, the probability of adverse effects with the combination of MDMA with MDEA was significantly lower than MDMA alone.

Discussion

This study demonstrates the large variation in the pharmacological content of tablets that were sold as ecstasy (MDMA) in The Netherlands between 2000 and 2010 and the related subjective effects experienced with these different tablets. However, it must be noted that the prevalence of the different pharmacological categories also



dose range (mg) % of MDMA alone	0-20 (3.1)	21-40 (6.2)	41-60 (16.7)	61-80 (28.8)	81-100 (19.0)	101-120 (10.7)	121-140 (8.9)	141-160 (3.9)	161-180 (2.1)	>180 (0.5)
desirable	0.18	0.29	0.66	0.83	0.88	0.81	0.75	0.62	0.36	0.01
adverse	0.05	0.05	0.04	0.05	0.06	0.08	0.15	0.21	0.55	0.86

Fig. 2 Dose–effect relationship of MDMA with adverse and desirable effects. *P(effect)* probability of the effect. *Odd ratio's significantly different from 1 in logistic regression ($p<0.05$, two-tailed)

varied greatly and that some of the categories only occurred in small batches of marketed ecstasy tablets. It is also noteworthy that desirable subjective effects (60%) were more prevalent than undesirable (adverse and lack of effects), suggesting that participants in this study did not necessarily hand in their drugs for analysis for reasons of discontent or health concern based on previous negative or worrisome experiences.

Overall, the results in this study show why MDMA has been such a successfully marketed recreational party drug over such a long period of time: MDMA has the highest probability of a desirable effect and a low probability of adverse effect, and no other substance or combination of substances matched MDMA's profile in terms of these subjective effects. Furthermore, all subjective effects of ecstasy that were reported by the participants in this study have been reported before by others, such as nausea, hallucinations, headache, palpitations, dizziness but also euphoria, relaxation and arousal (Peroutka et al. 1988; Liechti et al. 2001; Baylen and Rosenberg 2006; Sumnall et al. 2006; Kolbrich et al. 2008). In those studies the incidence of serious adverse effects or reactions has been reported to be relatively low and this was confirmed by the small proportion of such effects reported in this study

Table 3 Linking subjective effects to ecstasy tablets containing only one psychoactive substance

	Probability			OR (95% CI)	
	N	Desirable effect	Adverse effect	Desirable effect	Adverse effect
MDMA[a]	4,044	0.74	0.08		
MDA	107	0.24	0.39	**0.11 (0.07–0.18)**	**7.60 (5.07–11.39)**
MDEA	33	0.64	0.03	0.61 (0.30–1.24)	0.37 (0.05–2.70)
amphetamine	88	0.09	0.27	**0.04 (0.02–0.07)**	**4.41 (2.72–7.15)**
mCPP	614	0.09	0.59	**0.03 (0.02–0.04)**	**17.12 (14.05–20.90)**
mCPP+metoclopramide	126	0.23	0.17	**0.10 (0.07–0.16)**	**2.35 (1.45–3.80)**
caffeine	42	0.26	0.07	**0.12 (0.06–0.25)**	0.90 (0.28–2.94)
2 C-B	74	0.23	0.22	**0.10 (0.06–0.18)**	**3.24 (1.84–5.71)**
mephedrone	85	0.64	0.06	0.61 (0.39–0.95)	0.74 (0.30–1.83)
p-fluoroamphetamine	35	0.59	0.14	0.53 (0.27–0.70)	1.96 (0.76–5.09)
BZP	95	0.05	0.25	**0.02 (0.01–0.05)**	**3.97 (2.47–6.40)**

Odds ratios significantly different from 1.00 ($p<0.05$ two-tailed) are shown in bold

[a]Reference category in the logistic regression is MDMA

Table 4 Linking subjective effects to ecstasy tablets containing combinations of psychoactive substances

	Probability			OR (95% CI)	
	N	Desirable effect	Adverse effect	Desirable effect	Adverse effect
MDMA[a]	4044	0.74	0.08		
MDMA+PMMA	70	0.11	0.56	**0.05 (0.02–0.09)**	**14.79 (9.10–24.03)**
MDMA+mCPP	114	0.24	0.47	**0.11 (0.07–0.17)**	**10.22 (6.95–15.02)**
MDMA+MDEA	146	0.70	0.01	0.81 (0.56–1.16)	**0.16 (0.04–0.66)**
MDMA+amphetamine	65	0.50	0.08	**0.34 (0.21–0.55)**	0.98 (0.39–2.46)
MDMA+MDA	39	0.67	0.03	0.70 (0.36–1.36)	0.31 (0.04–2.26)

Odds ratios significantly different from 1.00 ($p<0.05$ two-tailed) are shown in bold

[a]Reference category in the logistic regression is MDMA

(0.9%). And, despite the lack of validated questionnaires in this study, the results on subjective effects in this study are in good agreement with previous studies using measures like the Visual Analogue Scales (VAS) or Profile of Mood States (POMS) (Dumont and Verkes 2006). Similar to the current study, in laboratory controlled studies, desirable effects were most prevalent with the typical recreational doses, whereas adverse reactions tended to rise with high doses of MDMA (Tancer and Johanson 2001, 2003; Baylen and Rosenberg 2006; Dumont and Verkes 2006). High dose MDMA tablets have been known to be dangerous for both unsuspecting and first time users, possibly leading to acute serotonin syndrome reactions like extreme hyperthermia (Parrott et al. 2002). In addition, these studies have shown that cardiovascular effects started to occur with MDMA doses between 1.0 and 2.1 mg/kg (Dumont and Verkes 2006); doses that correspond very well to the high doses where adverse effects started to emerge in this study (>120 mg/tablet).

With regard to the MDMA-like substances, tablets containing MDEA and combinations of MDMA with MDEA showed similar effects to MDMA alone, which is in line with previous research on this substance (Hermle et al. 1993; Gouzoulis-Mayfrank et al. 1999; Hegadoren et al. 1999). Interestingly, in the present study, MDA alone showed a decreased likelihood of desirable effects and an higher likelihood of adverse effects. A possible explanation could be that MDA has greater potency and a longer duration of effect compared to MDMA or MDEA (Kalasinsky et al. 2004; Morefield et al. 2011). By contrast, the combination of MDMA with MDA showed a desirable profile with few adverse effects. This might be related to some interaction between these two analogues or an additive effect of MDA to MDMA; the MDMA dose was quite low in these tablets (56.8 mg) compared to the tablets with MDMA alone (82.5 mg) and any resulting lack in stimulatory effects might have been compensated for by the addition of low amounts of MDA.

Psychoactive substances that were increasingly reported in tablets sold as ecstasy or in "party pills" are piperazine derivatives, mainly BZP and mCPP (Maurer et al. 2004; Tanner-Smith 2006; Antia et al. 2009; Bossong et al. 2005, 2010; Cohen and Butler 2010; EMCDDA 2010; Lin et al. 2011). Adverse effects after ingestion of mCPP were already described by others (Tancer and Johanson 2001, 2003; Feuchtl et al. 2004; Gijsman et al. 2004; Bossong et al. 2010). In the present study mCPP proved to be a very poor substitute for MDMA with a very high probability of adverse effects (59%). Confirming previous findings, nausea was the most frequent adverse effect associated with mCPP or its combination with MDMA. Interestingly, the likelihood of adverse subjective effects of mCPP almost disappeared when metoclopramide was added to tablets containing mCPP. Metoclopramide is a mixed dopamine D_2 and serotonin 5-HT_3 antagonist and is clinically applied as an anti-emetic drug in the treatment of nausea caused by various conditions (Cunningham 1997; Hiyama et al. 2009; Matok et al. 2009). Metoclopramide has also been proven effective against drug-induced nausea, but these studies did not include psychoactive drugs like mCPP (Bytzer and Hallas 2000). Interestingly, mCPP is a potent 5-HT_3 activator and the results presented here strongly suggest nausea being induced through the 5-HT_3 receptor, with subsequent antagonism by concurrent metoclopramide ingestion (Glennon et al. 1989; Higgins and Kilpatrick 1999). Although the producers were effective in reducing the adverse subjective effects of mCPP through the addition of metoclopramide, this new combination failed to produce significant desirable properties.

Adverse events of BZP in drug users have been described previously by other groups (Butler and Sheridan 2007; Johnstone et al. 2007; Thompson et al. 2010). On the other hand, similarity between subjective effects of BZP and MDMA was suggested in studies done with healthy volunteers (Lin et al. 2009, 2011). The results of the present study indicate that BZP's subjective effects are not similar to MDMA, and BZP was mainly associated with a decreased likelihood of desirable effects and an increased likelihood of adverse subjective effects in ecstasy users. However, most studies on subjective effects of BZP were

done in healthy, drug-naive volunteers and doses were not determined in the present study, important factors which might contribute to the differences in effects found and make comparisons difficult.

The adverse subjective effects reported in this study after ingestion of tablets containing MDMA with PMMA largely support the existing toxicological findings by others of casualties and fatalities after consumption of PMMA or its metabolite PMA (Caldicott et al. 2003; Johansen et al. 2003; Becker et al. 2003; Lin et al. 2007). Extreme hyperthermia was described as one of the symptoms of PMMA intoxication, especially in crowded environments (Rohanova and Balikova 2009; Páleníček et al. 2011). PMMA showed a more gradual peak concentration in the brain compared to MDMA, leading to a delayed pattern of activation and prolonged endurance of effects of the drug, with increased toxicity as consequence (Páleníček et al. 2011). Also, PMMA may inhibit serotonin reuptake in the brain more efficiently than MDMA, leading to extracellular serotonin accumulation (Callaghan et al. 2005). Moreover, a mixture of PMMA with MDMA, as described in this study, has been suggested to lead to increased and unpredictable toxicity as compared to either compound alone (Lora-Tamayo et al. 2004).

Mephedrone (4-MMC, "Meow Meow") is a relative newcomer on the Dutch ecstasy market (Brunt et al. 2010). In the current study, mephedrone had a desirable profile with a high probability of subjective desirable effects and a low probability of adverse subjective effects. Desirable subjective effects in drug users have been reported by a number of other studies in this field, but also by anecdotal reports on the internet (Brunt et al. 2010; Erowid 2010; Carhart-Harris et al. 2011; McElrath and O'Neill 2011; Winstock et al. 2011). Mephedrone is a substituted phenylethylamine, which action probably resembles that of amphetamine and methamphetamine (Brunt et al. 2010; Winstock et al. 2011). Its subjective effects are often described to be similar to ecstasy and cocaine, with stimulation and alertness, euphoria, intensity of senses and also empathy or sociability and talkativeness (Schifano et al. 2011). Adverse subjective effects were also described and largely resembled those of amphetamine or cocaine. However, in contrast to the current study, most studies reported effects in users that snorted the substance.

The recreational drug *p*-fluoroamphetamine (PFA, "Flux") has pharmacological properties distinct from amphetamine (Marona-Lewicka et al. 1995). In rats and in vitro, *p*-fluoroamphetamine resembles MDMA in its higher potency to release serotonin (5-HT) and lower potency to release dopamine (DA) compared to amphetamine (Marona-Lewicka et al. 1995; Wee et al. 2005; Nagai et al. 2007). In line with its 5-HT actions, users describe it as a mild MDMA (Erowid 2006). In the current study, *p*-fluoroamphetamine was associated with a relatively high probability of desirable subjective effects without a significant probability of experiencing adverse effects. By contrast, amphetamine itself did not show a desirable profile of subjective effects in the participants of this study. In the light of this, it is important to emphasize that participants were expecting an MDMA-like experience in all cases, which may well have impacted the subjective experience they reported on a different tablet, with amphetamine not resembling the (expected) effects of MDMA very closely.

Inherent to the design of this study, some limitations have to be mentioned. First of all, the DIMS is a system that is purposely anonymous because drug users would be deterred from using the testing facilities if personal details were an integral part of the testing session. Therefore, potential confounders could not be included in the logistic regression models (e.g., gender, age, psychosomatic history, education). Also, important information about the setting or polydrug use was lacking, which could have had an impact on the reported drug experiences. The findings are therefore within the boundaries of a strictly pharmaco-centric approach to drug-induced effects and need to be seen in the background of the complexity of the ecstasy market and all its various pharmacological appearances. Second, the study relies on the accuracy of participant's self-report and there was no way of confirming the actual use of the tablets they reported on. However, considering the sample size together with the consistency of the dose–response relationship of MDMA in this study suggests that most users had probably used the same tablets as they reported on. Furthermore, the frequency of desirable and undesirable subjective effects suggested that no selective bias for reporting sensational or worrying effects occurred. Finally, the quality of the reported information by drug users would be greatly improved by expanding the standard DIMS data with at least one standardized and validated questionnaire measuring subjective effects (Tancer and Johanson 2001, 2003).

In general, the results from this study provide strong evidence for the prolonged endurance of MDMA as the key ingredient of the ecstasy market, unrivalled by any other psychoactive substance addition or substitution. It thereby suggests that all attempts to create a better product, at least for the target population of ecstasy users in terms of its subjective effects, have failed thus far, and leaves MDMA to be the gold standard. This is an interesting finding in light of an ever growing attention towards emerging novel designer drugs and psychoactive substances (Europol-EMCDDA 2010). In light of this it is comprehensible that many potential substitutes for MDMA already left the market a long time ago (e.g., MBDB, MDEA, MDA, 4-MTA; EMCDDA 2003–2011). Further-

more, the findings from this study may help to understand differences in subjective effects of ecstasy found between studies from different countries and timeframes, when ecstasy tablets were of varying purity and/or composition. Considering the substantial differences in effects associated with the different pharmacological content in ecstasy tablets, it remains important to continue monitoring the markets of illicit drugs.

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