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4-Bromo-2,5-dimethoxyphenethylamine (2C-B): presence in the recreational drug market in Spain, pattern of use and subjective effects

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Abstract

4-Bromo-2,5-dimethoxyphenethylamine (2C-B) is a psychoactive analogue of mescaline that is becoming increasingly popular as a rave and club drug. We investigated its presence in the illicit drug market in Spain, its pattern of use and profile of subjective effects. Drug material was analysed for 2C-B and information on pattern of use and subjective effects was obtained from recreational users. Scores were statistically compared with previously collected data on psychostimulants (*d*-amphetamine), entactogens (MDMA) and psychedelics (ayahuasca and *Salvia divinorum*). The percentage of samples containing 2C-B doubled between 2006 and 2009, evolved from powder to tablet form and showed low falsification rates. Respondents reported taking 2C-B orally in doses of about 20 mg. Subjective effects involved perceptual modifications analogous to those observed after ayahuasca and salvia but absent after amphetamine and MDMA. Pleasure and sociability effects did not differ from those after MDMA and incapacitation was lower than for the psychedelics used as comparators. In conclusion, we found 2C-B is consistently present in the illicit drug market in Spain. While it elicits perceptual modifications that are analogous to other psychedelics, the lower impairment and higher pleasurable effects make it comparable with entactogens.

Keywords

2C-B, designer drugs, pattern of use, club drugs, subjective effects

Introduction

Amphetamine and phenethylamine derivatives are currently the synthetic drugs with the highest prevalence of abuse worldwide, particularly among young adults (European Monitoring Center for Drug Addiction, 2009a; United Nations Office on Drugs and Crime, 2010). Until recently, recreational use of this family of substances, named designer drugs, had revolved around a few compounds, mainly 3,4-methylenedioxymethamphetamine (MDMA, ecstasy), methamphetamine (ice, crystal) and amphetamine, although at least 200 different synthetic phenethylamines and tryptamines have been synthesized and their psychoactivity described (Shulgin and Shulgin, 1991, 1997). All these compounds could potentially reach the illicit market as recreational drugs, and there is evidence of increases in their use, at least for some compounds. Drugs such as 2,4,5-trimethoxyamphetamine (TMA-2), 2,5-dimethoxy-4-propylthiophenethylamine (2C-T-7), 2,5-dimethoxy-4-ethylthiophenethylamine (2C-T-2), 4-bromo-2,5-dimethoxyamphetamine (DOB), 4-hydroxyisopropyltryptamine (4-OH-DIPT), 4-acetoxydiisopropyltryptamine (4-ACO-DIPT), 4-methylthioamphetamine (4-MTA) and 4-methylmethcathinone (mephedrone) have been detected in Europe and the United States over the last decade (Andreasen et al., 2009; de Boer and Bosman, 2004; Johansen et al., 2003; Pichini et al., 2008; Roussel et al., 2009; Sanders et al., 2008; Voorspoels et al., 2002; Wood et al., 2009), and in some cases have been linked to serious adverse reactions and even fatalities (Ambrose et al., 2010; Andreasen et al., 2009; Carmo et al., 2007; Curtis et al., 2003; Huang and Bai, 2011; Johansen et al., 2003; Roussel et al., 2009; Tanaka et al., 2006; Wood et al., 2009; Voorspoels et al., 2002). Users typically use Internet websites and forums as sources of information on these substances, which can be easily purchased

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on-line (Drug Enforcement Administration, 2003; Takahasi et al., 2008).

4-Bromo-2,5-dimethoxyphenethylamine (2C-B, Nexus, Afro) is one of these synthetic drugs. At the chemical level, 2C-B is structurally related to mescaline and was first synthesized in the mid-1970s (Shulgin and Carter, 1975). It gained certain popularity as a legal substitute for MDMA after its prohibition in 1985 (Bouso et al., 2008). In some European countries 2C-B was legally sold as an aphrodisiac under the brand names Nexus, Erox and Performax in stores specialized in psychoactive products, the so-called smart shops (US Department of Justice, 2001). Internationally, 2C-B is a Schedule II drug under the Convention on Psychotropic Substances (International Narcotics Control Board, 2003). 2C-B was legal in most countries until the mid-1990s, when it became a controlled drug in most countries (Erowid, 2009). 2C-B has been intermittently detected in the illegal drug market in several countries over the last two decades (Bell et al., 2000; Giroud et al., 1998; Soares et al., 2004).

To date, very little scientific research has been conducted on 2C-B. The drug is known to be orally active and its effects are mediated by its action as a partial 5-HT_{2A} and 5-HT_{2C} receptor agonist. In addition, 2C-B is a substrate and an inhibitor of the serotonin transporter (SERT) (McLean et al., 2006; Montgomery et al., 2007). Regarding its psychotropic properties, 2C-B has been reported to induce 'perceptual enhancement' and euphoria at doses of 8–10 mg but to lack hallucinogenic or psychotomimetic effects (Shulgin and Carter, 1975). These authors also stated that the effects last 6–8 h and that they are milder than those of classical psychedelics such as lysergic acid diethylamide (LSD). More recent studies have addressed its metabolism in various animal species (Carmo et al., 2005; Kanamori et al., 2005; Rohanová et al., 2008), and several analytical methods have been developed to determine 2C-B in biological fluids (Pichini et al., 2008; Wohlfarth et al., 2010).

Regarding current prevalence and pattern of use, very little information is available dealing specifically with 2C-B, despite the efforts of several organizations such as the European Monitoring Center for Drugs and Drug Addiction (2003), and the EU-funded Psychonaut Web Mapping Project (2010), which was specifically developed to identify new recreational drugs.

The goals of the present study were to: a) investigate the presence of 2C-B in the illicit drug market in Spain; b) describe its patterns of use among recreational drug users; and c) assess its profile of subjective effects.

Methods and materials

Assessment of the presence of 2C-B in the illicit drug market in Spain

Drug material received between January 2006 and December 2009 was tested by the drug analysis service at *Energy Control*. This Spanish non-governmental organization (NGO), which works in the field of risk and harm reduction among recreational drug users, allows users to submit samples of their drugs to a central facility to have their content tested, and to obtain information and advice on risk reduction. All samples received were tested for 2C-B, MDMA, amphetamine, cocaine, ketamine and common adulterants such as caffeine.

Analytical procedures

2C-B was identified through a combination of validated analysis techniques. To detect 2C-B and check for potentially toxic adulterants we used two chromatographic techniques: thin layer chromatography (TLC) at *Energy Control*'s facilities, and gas chromatography associated with mass spectrometry (GC/MS) at the IMIM (Institut de Recerca Hospital del Mar – Parc de Salut Mar, Barcelona). With the TLC technique, analytes were identified by comparing their position (retention factor) and their colour in the Marquis test with those of a reference standard.

To confirm TLC results, samples were analysed using the GC/MS technique. GC/MS analysis was performed in an Agilent 5890 series II gas chromatograph coupled to a 5971A quadrupole mass spectrometer detector (Agilent). The gas chromatograph was fitted with an 6890 auto sampler injector. Samples were injected in split mode into a 12 m × 0.2 mm i.d., 0.33 µm film thickness 5% phenylmethylsilicone column (ULTRA-2, Agilent Technologies). The oven temperature was initially maintained at 90°C for 2 min and programmed to reach 300°C at 20°C per min. It was finally maintained at 300°C for 4 min, the total run time being 14.5 min. Insert liners packed with silanized glass wool were used. The injector and the interface were operated at 280°C. Helium was used as carrier gas at a flow rate of 0.48 mL/min. The mass spectrometer was operated in electron impact ionization mode at 70 eV. Qualifying ions selected for analytes under investigation were: m/z 215, 230 and 259. To confirm the mass spectra, the 2007 Wiley-VCH Verlag GmbH & Co. KgaA., Weinheim (Germany) reference library was used.

Ultraviolet spectrophotometry was performed in a Jenyway 6405 apparatus to determine the purity of the samples.

Assessment of the pattern of use and subjective effects of 2C-B

Participant sample. Participants were recruited from among 2C-B users who had submitted their samples for analysis between January 2006 and December 2009. After verifying the presence of authentic 2C-B in the drug material by means of the aforementioned analytical techniques, users were invited to participate in a study evaluating their pattern of use of 2C-B and the subjective effects elicited by the drug. Users contacted were those who had submitted samples containing 2C-B without any other psychoactive substance present. They were contacted by email, and selected based on their having at least one experience in which 2C-B was consumed in the absence of other drugs. Volunteers who fulfilled this condition were sent a battery of three self-report questionnaires (see below). They were not paid for their participation but, like all customers who submit samples to *Energy Control*, they were given the results of the analysis, plus risk reduction information and advice. The study was approved by the Ethics Committee of the Hospital de Sant Pau. All volunteers gave their written informed consent to participate.

Self-report instruments. A battery of three written questionnaires was used. Participants were asked to respond to questions, recalling the effects they had experienced when they last took 2C-B alone, i.e. not combined with any other drug.

The first questionnaire was specifically designed for this study. It collects socio-demographic data (age, gender and level of education), prior experience with other drugs, number of consumptions of 2C-B, route of administration, consumption context, used doses, duration of the experience, drug source, simultaneous use with other drugs and satisfaction with the experience. The questionnaire includes three lists of 15 questions to which participants have to give yes/no answers to characterize the experienced acute psychological effects, acute adverse effects and subacute adverse effects, i.e. those occurring within 48 h of consumption. The items included in the lists were selected from: a) previous studies assessing MDMA and psychedelics (Greer and Tolbert, 1986; Grob et al., 1996; Liester et al., 1992); b) reports of experiences with 2C-B found in magazines and books (Bouso, 2003; Capdevila, 1995; Escohotado, 2003; Holland, 2001; Ott, 1993; Shulgin and Shulgin, 1991); and c) self-reports, i.e. the so-called 'trip reports' available on Internet websites such as www.erowid.org, www.lycaeum.org and www.bluelight.ru. After reviewing this material, three of the authors (FC, JCB and MV) independently developed three lists of 15 potential questions that were discussed in several meetings until a consensus was reached and the final 15 items were agreed upon. In addition, participants were given the option to report any 'other adverse effects' not listed in questionnaire.

The other two questionnaires included in this study are specific psychometric tests designed and validated to assess the subjective effects of psychoactive drugs: the Hallucinogen Rating Scale (HRS) (Strassman et al., 1994) and the Valoración de Efectos Subjetivos de Sustancias con Potencial de Abuso – Evaluation of the Subjective Effects of Substances with Abuse Potential Questionnaire (VESSPA) (Poudevida et al., 2003). Information on subjective effects was obtained by means of the retrospective assessment of drug effects when they last took 2C-B alone (i.e. without combining it with other drugs).

The HRS was translated and validated into Spanish by Riba et al. (2001a). The questionnaire has been used to assess the subjective effects of the hallucinogen ayahuasca (Barbanoj et al., 2008; Riba et al., 2001b, 2003, 2006), ketamine (Krupitsky et al., 2002), psilocybin, 3,4-methylenedioxyethylamphetamine (MDE), methamphetamine (Gouzoulis-Mayfrank et al., 1999), dimethyltryptamine (DMT) (Strassman et al., 1994), *Salvia divinorum* (González et al., 2006) and *d*-amphetamine (Barbanoj et al., 2008). It has 71 Likert items distributed in six scales: 'Somaesthesia' (reflecting somatic effects), 'Affect' (sensitive to emotional and affective responses), 'Volition' (indicating the person's degree of impairment), 'Cognition' (describing changes in thought process or content), 'Perception' (measuring visual, olfactory, gustatory and auditory experiences), and 'Intensity' (reflecting the strength of the overall experience).

The VESSPA was originally designed to measure the subjective effects of MDMA, but has also been used to measure the psychopharmacological effects of other substances such as cocaine, cannabis, LSD, alcohol (Poudevida et al., 2003), and GHB and flunitrazepam (Abanades et al., 2007). It has 36 Likert items, which are grouped in six scales: 'Sedation' (SED), 'Psychosomatic anxiety' (ANX), 'Changes in perception' (PER), 'Pleasure and sociability' (SOC), 'Activity and energy' (ACT) and 'Psychotic symptoms' (PSY).

To better characterize the profile of subjective effects induced by 2C-B, scores on the HRS and the VESSPA were statistically compared with data obtained by our group in: a) a clinical trial involving the administration of 20 mg *d*-amphetamine and ayahuasca equivalent to 1.0 mg *N,N*-dimethyltryptamine (DMT)/kg body weight (data from 18 participants); b) a clinical trial involving the administration of 100 mg MDMA; and c) a survey study in which salvia users were asked to retrospectively report the subjective effects they experienced when they last took the drug (data from 32 participants). Subjective effects data from these studies have been published for the HRS (Barbanoj et al., 2008; González et al., 2006) but not for the VESSPA or HRS in the case of MDMA (Hernández-López et al., 2002).

Statistical analysis. Demographic data and data from the first questionnaire are descriptive in nature, and accordingly, descriptive statistics are provided in the results section. Absolute numbers and percentages are reported for categorical variables and means and standard deviations (SD) for continuous variables.

Summary data (mean values) are also presented for the HRS and VESSPA scores in graph format. In addition, inferential statistics are used to compare the scores obtained in the present study with those from previous laboratory (*d*-amphetamine, ayahuasca, MDMA) and survey (salvia) studies. Scores were compared by means of a one-way ANOVA with drug (2C-B, amphetamine, ayahuasca, MDMA, salvia) as factor. When the ANOVA yielded a significant result, pairwise comparisons were performed by means of Tukey's test. Only the results of the following three comparisons are shown: 2C-B vs. d-amphetamine, 2C-B vs. ayahuasca, 2C-B vs. MDMA, 2C-B vs. salvia. Results were considered statistically significant for p values lower than 0.05.

Results

Presence of 2C-B in the illicit drug market in Spain

Table 1 shows the results of the analyses performed by the NGO *Energy Control* between January 2006 and December 2009. All samples received were tested for 2C-B, MDMA, amphetamine, cocaine, ketamine, other research chemicals (phenethylamine, amphetamine, tryptamine and cathinone derivatives) piperazines, such as m-CPP, and common adulterants such as caffeine, acetaminophen, phenacetin, levamisole, metoclopramide, local anaesthetics, and all compounds included in the 2007 Wiley-VCH Verlag GmbH & Co. KgaA., Weinheim (Germany) reference library. Over the 4-year period, 97 of 3303 samples were received purportedly contained 2C-B. 2C-B was detected in 96 samples (99%). The other sample contained 4-iodo-2,5-dimethoxyphenethylamine (2C-I) rather than of 2C-B. Of the 96 confirmed 2C-B samples, 52 (54%) were in tablet form and the remaining 44 (46%) were in powder form or encapsulated. Of the 52 tablets, four (8%) were detected in the first two years (between January 2006 and December 2007), 10 (19%) in the third year (2008) and 38 (73%) in the fourth year (2009). In 93 samples (97%) 2C-B was the only psychoactive compound detected. Two tablets from two different users contained 2C-B and caffeine, and in one powder sample diazepam was found in addition to 2C-B. No other adulterants were detected. Of all the samples testing positive for psychoactive substances, 2C-B represented only 2.61% in 2006, increasing to 5.14% in 2009. Analogously, the presence of other research chemicals increased from 1.74% to 5.76% in the same 4-year period. In contrast, samples that were positive for MDMA decreased from 61% to around 39% of the total.

Table 1. Samples analysed

	2006			2007			2008			2009			Variation	
Drug	n1	n2	%	n1	n2	%	n1	n2	%	n1	n2	%	n2	%
MDMA	242	141	61.30	252	196	50.65	488	422	51.21	840	375	38.54	+234	–22.76
Amphet	46	40	17.39	84	69	17.83	166	147	17.84	206	180	18.50	+140	+1.11
Cocaine	41	34	14.78	118	104	26.87	192	167	20.27	289	265	27.24	+231	+12.45
Ketamine	6	5	2.17	8	8	2.07	26	24	2.91	49	47	4.83	+42	+2.66
2C-B	6	6	2.61	6	6	1.55	34	34	4.13	51	50	5.14	+44	+2.53
RCs	5	4	1.74	4	4	1.03	32	30	3.64	66	56	5.76	+52	+4.02
Total	392	230		472	387		938	824		1501	973		+743	

n1 = number of samples received supposedly containing a given drug; n2 = number of samples which actually contained a given drug; % = percentage amongst positives. Amphet, Amphetamine; RCs, Other research chemicals (phenethylamine, amphetamine, tryptamine and cathinone derivatives combined).
Number of samples received and results obtained in the qualitative analyses performed by the drug analysis service of the non-governmental organization *Energy Control* between 2006 and 2009. For each year three values are given: 1) the left column shows the number of samples received purportedly containing a given drug; 2) the centre column shows the number of samples which actually contained a given drug, i.e. the number of true positives; and 3) the right column indicates the percentage of a positively identified drug amongst all true positives (centre column). The two 'Variation' columns indicate change between 2006 and 2009 in total number and in percentage.

Table 2. Types of 2C-B tablets analysed between June and December 2009

Picture	Logo	Colour	Size	Dose	Region	No Tablets
	Mickey Mouse	Blue	7.21 × 2.91	9.04 (0.29)	Madrid, Andalusia, Catalonia, Navarre	10
	Mickey Mouse	Pink	7.18 × 2.57	8.46 (0.44)	Andalusia, Madrid, Balearic Islands, Navarre	6
	Rolex	Green	------	7.2 (0.14)	Madrid	2
	2C-B	White	7 × 2.74	8 (2.8)	Catalonia, Madrid	4
	Amanita muscaria	Blue	6.77 × 2.65	10.25 (0.18)	Madrid	2

Sizes are given in mm and doses in mg expressed as mean (SD).

The frequency of falsification for 2C-B was low. Of the received samples, 99% contained the drug (average for the 4-year period). This figure compares with 66.8% for MDMA, 86.3% for amphetamine, 87.4% for cocaine, 92.9% for ketamine and 89.7% for other research chemicals. MDMA thus showed the highest levels of falsification, with many samples containing meta-chlorophenylpiperazine (m-CPP) instead. This phenomenon was mainly observed in 2006 and 2009.

Quantitative analyses were conducted in 2008 and 2009. In 2008 mean (SD) 2C-B content was 15.5 (10.27) mg and in 2009 it was 8.59 (1.21). Table 2 shows the most frequently encountered tablet types in the second half of 2009 and their quantitative contents. Interestingly, identical tablet 'brands' were received from geographically distant regions in Spain and the 2C-B content of each 'brand' was surprisingly uniform over the 6-month study period (see the low SD values for each tablet type). The

'Mushroom', 'Crown' and 'Mickey Mouse' brands were specific for 2C-B. However, the 'Rolex' brand is less specific and it has been found in MDMA-containing pills.

It is worth mentioning that 2C-B was detected in four samples purportedly containing MDMA and in one sample purportedly containing mescaline

Demographic characteristics of the participant sample

We recruited 52 users who acknowledged having consumed 2C-B at least on one occasion. Of the 52, 38 returned correctly completed questionnaires (73%). Three of the 38 respondents reported that the last time they had used 2C-B they had combined it with another drug (MDMA, ketamine and LSD). They were consequently excluded from the study to ensure that the information gathered, especially regarding subjective effects, referred to 2C-B only. Thus, the final sample consisted of 35 individuals, 27 (77%) of whom were male and eight (23%) female. The mean age of the sample was 32.6 years (SD: 6.53; range: 21–45 years). At the time of assessment, 25 (71%) participants were attending university or had a university degree.

Participants showed high rates of illicit drug use in the previous month: 24 (69%) had used cannabis, 10 (29%) ecstasy (MDMA), six (17%) speed (amphetamine) and six (17%) cocaine. In all, 34 participants (97%) had used cannabis at some time, 34 (97%) had also used MDMA, 31 (83%) had used cocaine, 28 (80%) LSD, 26 (74%) hallucinogenic mushrooms, 24 (69%) speed (amphetamine), 16 (46%) ayahuasca, 14 (40%) ketamine and 13 (37%) *Salvia divinorum*.

Self-report questionnaires: pattern of 2C-B use and subjective effects

Participants had used 2C-B on a lifetime average of 4.4 (SD: 4.2) occasions (mean 2.0, SD: 2.0, during the last year). In all, 26 subjects (74%) had used 2C-B between one and four times; three (9%) between five and eight times; four (11%) between nine and 12 times; and two (6%) more than 12 times. All participants had used 2C-B in the previous month. Thirty participants (85%) responded they intended to use 2C-B again in the future, 16 (47%) in the following year, 12 (32%) in following month and two (6%) in the following week.

Most of the participants ($n = 25$; 71%) had obtained 2C-B from drug dealers. Nevertheless, 20 subjects (57%) mentioned having used the Internet at least once to purchase 2C-B. Information on habitually used doses was only provided by 31 subjects (89%), who reported an average dose of 21 mg (SD: 11.7). Some 74% ($n = 23$) of the sample reported using regular doses equal to or lower than 20 mg. Three individuals reported using doses between 40 and 60 mg.

Most participants took the drug orally; 74% ($n = 26$) had only used this route. Intranasal use was used, at least occasionally, by 23% of participants ($n = 9$) at doses of 10–30 mg. None of the participants reported having smoked the drug or having used it intravenously.

Twenty-nine participants (83%) stated that they had taken 2C-B simultaneously with other drugs, most commonly in combination with MDMA (69%; $n = 24$), alcohol (43%; $n = 15$) and cannabis (40%; $n = 14$). Five subjects (14%) had combined 2C-B with ketamine, another five with hallucinogenic mushrooms, and four participants (11%) had combined it with speed (amphetamine). Despite having combined 2C-B with another drug at some point, the reports gathered on subjective effects (see below) referred to the last time they took 2C-B in the absence of any other drug.

Typical settings of use were recreational environments (clubs, parties and raves) (60%; $n = 21$), followed by home use with friends (54%; $n = 19$), at home with a partner (37%; $n = 13$) or in the countryside (20%; $n = 7$). When users were asked about the ideal setting to use 2C-B, the most frequent answers were: 'at home with partner' (65%; $n = 23$), 'at home with friends' (60%, $n = 21$) and 'strolling or in the countryside' (60%; $n = 21$). Only 29% ($n = 10$) of the sample chose recreational settings like clubs, parties and raves as the ideal setting.

Regarding subjective effects, the survey questionnaire contained items on the time course and nature of the 2C-B experience. Participants reported a mean duration of effects of 6.2 h (SD:1.2), a lag time after ingestion of 1.2 h (SD:0.5) and a time to maximum effects of 2.5 h (SD:1.1). Concerning the characteristics of the effects felt, Table 3 lists the number and percentage of participants who responded positively to the items included in the questionnaire. Changes in tactile, visual and auditory perception were the most frequently reported effects. Physical sensations, changes in thought, time perception and emotion were reported less

Table 3. Acute subjective effects elicited by 2C-B

Items	*n*	%
Sense of touch and perception of own body are enhanced	26	74
The walls and floor move about in waves	23	66
Colours and shapes become more distinct	21	60
Sounds and music become more distinct	20	57
With eyes closed I can see images (geometrical patterns, shapes)	20	57
I have an intense feeling of peace and wellbeing	19	54
Everything seems unusually funny and makes me laugh	17	49
Halos or auras can be seen around objects	16	46
Things happen slower than usual	14	40
Objects seem to move	14	40
I feel very sensitive to cold and heat	13	37
Thoughts come to mind faster than usual	12	34
With eyes open I can see images (geometrical patterns, shapes)	11	31
I find it easier to communicate with others	11	31
I have strange and unusual thoughts	10	29
With eyes open I can see things that are not real	8	23
I feel like having sex	8	23
Objects seem larger or smaller than usual	7	20
My thoughts are more clouded and slower	6	17
I'm aware of things that I did not remember before	6	17
I feel distressed	6	17
Any discomfort or small pain is greater	5	14
Things happen faster than usual	4	11
I'm afraid	4	11

The table shows the number and percentage of participants who responded affirmatively to the items included in the questionnaire.

frequently. Some 74% (n = 26) of the sample reported having experienced some unpleasant effect during the acute 2C-B experience (see Table 4). One unpleasant effect was reported by 31% (n = 11), 11% (n=4) reported two and 17% (n = 6) reported three. The most common effects were trembling, sweating and difficulty focusing gaze. Some 43% (n = 15) reported residual effects (RE) lingering until up to 48 h after 2C-B intake; 23% (n = 8) reported one RE, 17% (n = 6) reported two REs and 3% (n = 1) reported three REs. Table 5 lists REs from most commonly to most rarely reported effects. The most frequently reported were insomnia and the involuntary reoccurrence of the experience or 'flashbacks'.

Table 4. Acute unpleasant effects elicited by 2C-B

Items	*n*	%
Difficulty focusing gaze	13	37
Trembling	9	26
Sweating	8	23
Nausea	5	14
Pain in stomach and belly	5	14
Tachycardia	4	11
Jaw clenching	4	11
Difficulty breathing	3	9
Cough	3	9
Diarrhoea	3	9
Dizziness	2	6
Muscle or joint pain	2	6
Pins and needles in arms or legs	1	3
Urge to defecate, urinate	1	3
Headache	1	3
Paresthesia	1	3
Stiff neck	1	3
Vomiting	0	0

The table shows the number and percentage of participants who responded affirmatively to the items included in the questionnaire.

Table 5. Residual effects of 2C-B during the 48 h following intake

Items	*n*	%
Insomnia	4	11
Involuntary reoccurrence of the experience ('flashbacks')	4	11
Anxiety	3	9
Cough	3	9
Difficulty concentrating	3	9
Depression or sadness	2	6
Lack of appetite	1	3
Headache	1	3
Sweating	1	3
Backache	1	3
Fear	0	0
Muscle or joint pain	0	0
Bad mood	0	0
Vomiting	0	0

The table shows the number and percentage of participants who responded affirmatively to the items included in the questionnaire.

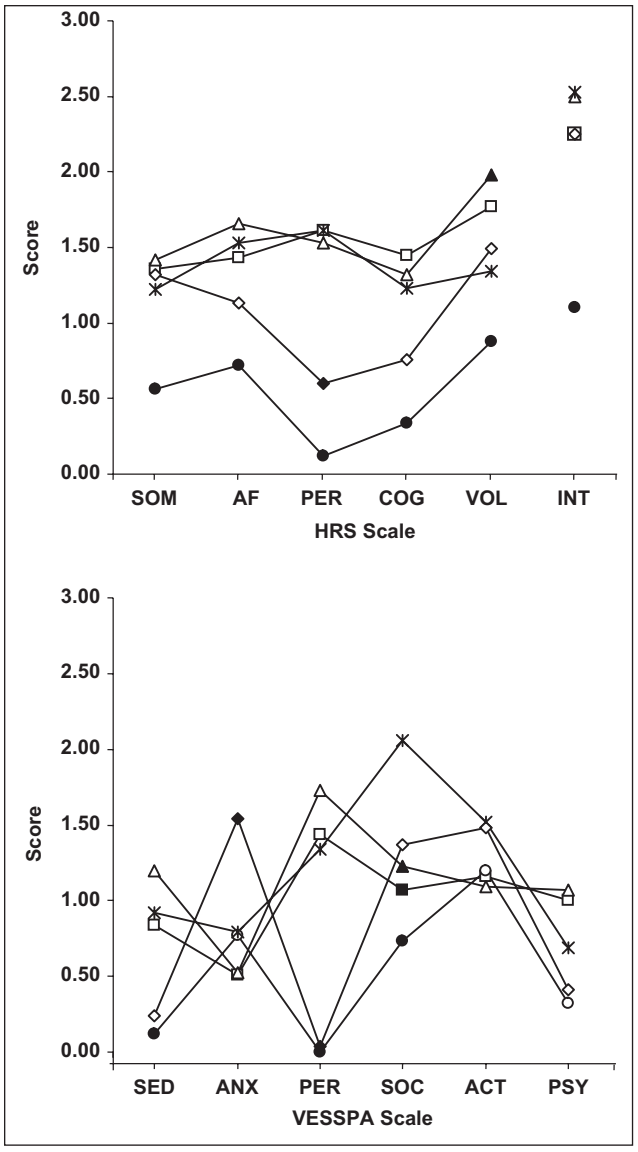

Figure 1. Upper panel: Mean scores on the HRS scales for 2C-B (star, n = 35), ayahuasca (square, n = 18), *d*-amphetamine (circle, n = 18), *Salvia divinorum* (triangle, n = 32) and MDMA (diamond, n = 9). Filled symbols indicate significant differences vs. 2C-B. Lower panel: Mean scores on the VESSPA scales for 2C-B (star, n = 35), ayahuasca (square, n = 18), d-amphetamine (circle, n = 18), Salvia divinorum (triangle, n = 32) and MDMA (diamond, n = 9). Filled symbols indicate significant differences vs. 2C-B.
SOM, Somaesthesia; AF, Affect; PER, Perception; COG, Cognition; VOL, Volition; INT, Intensity; SED, Sedation; ANX, Psychosomatic Anxiety; PER, Change in Perception; SOC, Pleasure and Sociability; ACT, Activity and Energy; PSY, Psychotic Symptoms

Scores on the HRS scales and results of the statistical analyses performed are shown in Figure 1, upper panel. The highest scores for 2C-B were obtained in the Perception scale and the lowest in the Somaesthesia scale. Compared with the pure psychostimulant *d*-amphetamine, 2C-B scores were statistically significantly higher in all scales. On the other hand, compared with the other two psychedelic drugs, ayahuasca and salvia, no statistically significant differences were found in the Somaesthesia, Affect,

Perception, Cognition and Intensity Scales. Statistically significant differences were found for the Volition scale only. Scores on this scale were higher than after amphetamine but lower than after ayahuasca and salvia. Mean scores on the Affect, Perception and Cognition scales after MDMA were higher than after amphetamine but lower than after 2C-B. Statistically significant differences between 2C-B and MDMA were found only in the Perception scale.

Scores on the VESSPA scales and results of the statistical analyses performed are shown in Figure 1, lower panel. The highest scores for 2C-B were obtained in the Pleasure and Sociability scale and the lowest in the Psychotic Symptoms scale. Pairwise comparisons showed that compared with amphetamine, 2C-B scored significantly higher in the Changes in Perception, Pleasure and Sociability, and Sedation scales. No significant changes were found in the Activity and Energy, Psychosomatic Anxiety and Psychotic Symptoms scales. Compared with ayahuasca, and salvia, 2C-B scored significantly higher in the Pleasure and Sociability scale. No significant differences were found in any other scale. Compared with MDMA, 2C-B scored significantly higher in the Changes in Perception scale and significantly lower in the Psychosomatic Anxiety scale. No other significant results were seen.

Discussion

Our study confirms the presence of 2C-B in the illicit market of recreational drugs in Spain. The number of samples analysed by *Energy Control* which tested positive for this compound showed an increasing tendency in the 4-year period studied. Previously, 2C-B had only been found sporadically (Gamella et al., 1999; Hidalgo, 2007). The rise from 2.6% to 5.1% supports the perception that, although it is still a minor drug, 2C-B is consistently accessible to users. This trend was also observed for other synthetic amphetamines, phenethylamines and tryptamines sold generically as 'research chemicals'. Positive identifications of these compounds rose in the same period from 1.7% in 2006 to 5.8% in 2009. However, 2C-B was more frequently detected than any of these substances. 2C-B samples were not falsified with other synthetic phenethylamines or piperazines, in contrast with MDMA samples, many of which contained m-CPP. In addition, the market appears to have gradually become more sophisticated and extended. Whereas in 2006 and 2007 the vast majority of the samples received appeared in poorly elaborated formats such as powder or capsules, in 2008 and 2009 the most frequent presentation form was tablets. Considering the frequently reported simultaneous use of 2C-B and MDMA, an explanation for this trend could be the fact that MDMA users are more familiar with tablets than with powder, and the presentation change may be intended to appeal to this population. It also suggests that 2C-B distribution may have become more professionalized, possibly now using the distribution channels used for ecstasy. The finding that the same tablet 'brands' were received from very distant regions in Spain and that the doses found for each 'brand' were very similar supports this suggestion and may also reflect the expansion of the illicit market. In line with this possibility, over 70% of respondents reported that drug dealers were their source of supply.

The large increase in the number of 2C-B samples received in 2008 and 2009 and their diverse geographical origin suggests that this 2-year period may have been one of relevant growth of the market. In line with this finding, in 2008 and 2009 2C-B was detected by NGOs in the illicit markets of other European countries such as Switzerland (Saferparty Warnungen, 2009). Since 2008, several reports of toxic effects caused by 2C-B have appeared both in the general media (Sherdley and Greenwell, 2009) and in the scientific literature (Ambrose et al., 2010; Huang and Bai, 2011), which again suggests increased access to 2C-B by recreational drug users. A possible factor influencing this increase is the shortage of ecstasy observed in the illicit market in Spain and other European countries (Carabaña, 2009; European Monitoring Center for Drug and Drug Addiction, 2009b; United Nations Office on Drugs and Crime, 2010). In the analyses we conducted, we found 2C-B in four samples purportedly containing MDMA, further linking 2C-B to a decrease in MDMA availability. Although a cause–effect relationship cannot be established based on the available data, the potential link highlights the importance of closely monitoring the illicit drug market in the search for changing trends in drug use and the appearance of new drugs.

To our knowledge this is the first study to report on the pattern of use and profile of subjective effects of 2C-B in a group of recreational users. Participants stated having used 2C-B on few occasions and at moderate doses. They had all begun taking 2C-B after having experimented with other synthetic drugs, particularly MDMA and LSD. An interesting finding was the large number of individuals who had taken 2C-B in combination with MDMA, again suggesting a common market for the two drugs.

Responses to the subjective effect questionnaires confirm reports describing 2C-B as a drug inducing psychedelic effects of medium duration, and a priori milder than those of more classical drugs such as LSD (Bouso, 2003; Holland, 2001). Detailed examination of the HRS results, nevertheless, shows that in terms of effects on the affective and perceptual spheres, scores were quite high, comparable with those obtained in clinical trials after doses of ayahuasca equivalent to 1.0 mg DMT/kg body weight (Riba et al., 2001b, 2006). However, average scores on the Cognition scale are indicative of milder effects on thought processes. This and the significantly lower scores obtained in the Volition scale, a measure of the subject's degree of incapacitation, could explain why effects after 2C-B are usually considered easier to handle than those of other psychedelics, despite the capacity of 2C-B to induce full-blown modifications in perception. Interestingly, scores on the Volition scale were similar to those obtained after MDMA. This compound showed a profile between that of a pure psychostimulant and the psychedelics. The results obtained show that 2C-B is clearly different from MDMA in its capacity to induce perceptual modifications.

An interesting aspect of the pattern of responses on the VESSPA questionnaire is the analogous scores obtained for *Salvia divinorum*, a kappa agonist-containing plant, and ayahuasca, a plant tea containing a 5-HT_{2A} agonist. Despite their different mechanisms of action, mean scores on all scales were quite similar, with the highest values obtained in the Changes in Perception scale followed by scores in the Pleasure and Sociability and in the Activity and Energy scales. Remarkably, the profile for 2C-B, in principle another psychedelic 5-HT_{2A} agonist, is quite different. Here the pattern is reversed, with the highest scores obtained in the Pleasure and Sociability and in the Activity and Energy scales followed by scores in the Changes in Perception scale. This same pattern has been reported for MDMA

(Poudevida et al., 2003), although MDMA additionally induced large increases in the Psychosomatic Anxiety scale, which 2C-B did not. In our study, the scores in Pleasure and Sociability scale were higher for 2C-B than MDMA. The two settings of the study, experimental administration in a clinical trial for MDMA versus self-reported retrospective experience for 2C-B, could explain the observed differences. Regarding drug liking, a majority of respondents in the present study (85%) said they would like to use 2C-B again in the future. This contrasts with data from a previous survey study on *Salvia divinorum* in which only 44% of participants manifested their wish to use salvia regularly (González et al., 2006). Again, this difference may reflect more controllable or desirable effects for 2C-B. Overall, the lower impairment produced by 2C-B as compared with other psychedelics and the higher scores obtained in pleasure and sociability may explain why most subjects had used 2C-B in party settings despite their belief that a safer, more quiet context would be preferable.

Participants also reported a series of acute unpleasant effects, some of which are possibly related to sympathetic activation. Thus, 'difficulty to focus', the most frequently reported undesirable effect, could be caused by alterations in visual accommodation due to mydriasis, as has been described for other serotoninergic drugs such as fenfluramine and MDMA (de la Torre et al., 2000; Griffith et al., 1975). With regard to residual effects, insomnia and anxiety could also be due to the drug's sympathomimetic properties. Interestingly, some volunteers reported a potentially more serious residual effect, i.e. 'flashbacks', or the spontaneous reoccurrence of some aspects of the experience. This phenomenon has repeatedly been associated with psychedelics (Halpern and Pope, 2003) and, based on a recent web-based survey (Baggott et al., 2011), it may be more frequent than previously thought. Unfortunately, due to limitations in participant availability, we were unable to conduct psychiatric interviews to check whether affected respondents met criteria for Hallucinogen Persisting Perception Disorder. This aspect of 2C-B pharmacology should be assessed in more detail in future studies.

It is also worth mentioning that although most participants had taken 2C-B orally, occasional intranasal use was reported by almost one third of the sample. This route of administration has been associated with fatal adverse events after the intake of synthetic phenethylamines structurally related to 2C-B, as is the case for 2-C-T-7, also known as 'blue mystic' (Curtis et al., 2003). However, apart from the few residual effects recorded, no serious adverse events were reported in our survey. Psychosis (Huang and Bai, 2011) and cerebral vasculopathy with severe incapacitation have recently been reported after intake of suspected 2C-B (Ambrose et al., 2010). The absence of severe adverse effects found in our study may be related to the characteristics of the sample and their limited exposure to the drug. Participants were mainly graduate students who were in their thirties and had a wide experience in the recreational use of psychotropic drugs. The moderate doses used, the low number of exposures, and the fact that they had approached *Energy Control*'s drug analysis service, suggest a relatively careful approach to drug taking. It should also be pointed out that the small size of our sample may have precluded the detection of infrequent but severe side effects. It is thus difficult to extrapolate our data to the general population and these results should be considered preliminary.

To summarize, the use of synthetic phenethylamines, and specifically 2C-B, is an as yet limited but consistent phenomenon. The drug displays psychological effects that are analogous to those of other perception-modifying drugs, although they produce less impairment and a higher degree of pleasurable effects. Nevertheless, the drug also shows relevant undesired effects which are suggestive of sympathetic activation. This is a matter of concern considering the common practice of its combination with other psychostimulants such as MDMA. Additional research is needed on the pharmacology of 2C-B in order to assess the potential health risks associated with its use alone and in combination with other drugs.

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Conflict of interest

The authors declare that there is no conflict of interest.

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