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4,4'-dimethylaminorex ('4,4'-DMAR'; 'Serotoni') misuse; a web-based study

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TITLE PAGE

Title: 4,4'-dimethylaminorex ('4,4'-DMAR'; 'Serotoni') misuse; a web-based study

Running head: 4,4'-DMAR on the web

Keywords: drug abuse; 4,4'-DMAR; aminorex derivatives; novel psychoactive substances; psychonauts; online fora; stimulants

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targeted call on cross border law enforcement cooperation in the field of drug trafficking - DG Justice/DG Migrations and Home Affairs (JUST/2013/ISEC/DRUGS/AG/6429) Project EPS/NPS (Enhancing Police Skills concerning Novel Psychoactive Substances; NPS).

Abstract

Background: 4,4′-DMAR (4,4'-dimethylaminorex; 'Serotoni') is a potent stimulant drug which has recently been associated with a number of fatalities in Europe. Over the last few years, online communities have emerged as important resources for disseminating levels of technical knowledge on novel psychoactive substances/NPS.

Objective: Analysing the information provided by the fora communities on 4,4'-DMAR use, additionally critical reviewing the available evidence-based literature on this topic.

Methods: Different website drug fora were identified. A critical review of the existing evidence-based literature was undertaken. Individuation and analysis of qualitative data from the identified website fora were performed.

Results: The combined search results identified six website fora from which a range of qualitative data on recurring themes was collected. These themes included: routes of administration and doses; desired effects; adverse effects; comparison with other drugs; association with other drugs; medications self-

administered to reverse 4,4'-DMAR action; overall impression; provision of harm reduction advice.

Conclusions: Although being characterized by a number of methodological limitations, the social networks' web monitoring approach (netnography) may be helpful to better understand some of the clinical and psychopharmacological issues pertaining to a range of NPS, including 4,4'-DMAR, for which only extremely little, if any, scientific knowledge is available.

Abbreviations

Novel psychoactive substances: NPS

Blood brain barrier: BBB

Dopamine transporter: DAT

Norepinephrine transporter: NET

Serotonin transporter: SERT

Route of administration: ROA

Introduction

Internet use has become an unremarkable aspect of everyday life, providing a revolutionary tool to facilitate rapid interpersonal communication, exchange of ideas, opinions, and information on a range of issues, including recreational drugs (Wax, 2002).

Overall, the web represents the most popular source of information about NPS use (Nelson et al., 2014). In this respect, web fora are being extensively used as discussion areas (Orsolini et al., 2015). A forum moderator often oversees the communication activities, whilst facilitating the debate, and making decisions regarding the direction of threads. Apart from drug enthusiasts, fora members may include researchers, harm-reduction specialists, police officers, lawyers, physicians, journalists and addiction specialists, all actively contributing to the debate (https://drugs-forum.com/index.php).

Although fora communities are virtual, these social groups can have consequential effects on many aspects of the member's behaviour (Kozinets, 2002) as the information being accessed may be misleading, or even dangerous, and particularly so for naïve users (Monahan & Colthurst, 2001).

With the increase in web marketing of drugs available for purchase, online discussions have, however, become a reason for concern as they could lead to an increase in drug using

levels (Soussan & Kjellgren, 2014) whilst playing a crucial part in raising interest about drugs (Griffiths et al., 2010).

4,4'-DMAR

4,4'-DMAR (Figure 1) (IUPAC: 4-methyl-5-(4-methylphenyl)-4,5-dihydrooxazol-2-amine), is a synthetic substituted oxazoline derivative which contains two chiral centres and two racemic mixtures (i.e. (±)-cis and (±) trans-racemates). Previous analytical characterizations confirmed that the (±)-cis racemate is the most available isomer in the market and the one involved in many deaths (Brandt et al., 2014). This stimulant drug is commonly advertised as 'para-Methyl-4-methylaminorex', '4-methyl-euphoria', '4-methyl-U4Eu', '4-M-4-MAR', '4,4-dimethylaminorex' and 'Serotoni'.

It belongs to the Novel Psychoactive Substance (NPS) category, which encompasses a wide number of compounds widely marketed in the 'real' and 'virtual' world as legal substitutes for banned drugs (Miliano et al., 2016) and being sometimes more harmful than their parental compounds in terms of toxicity, adverse reactions, dependence, long-term effects (Schifano et al., 2015), fatalities (Chiappini et al., 2015; Loi et al., 2015) and psychiatric consequences (Martinotti et al., 2014).

4,4'-DMAR was first detected in Europe in the Netherlands at the end of 2012, and by the first half of 2013 it had emerged in Denmark, Finland, Hungary, Poland, Romania, Sweden and the United Kingdom (EMCDDA and Europol, 2014; EMCDDA, 2015).

It is a research chemical most commonly sold over the Internet and head-shops in the form of powder and tablets, usually labelled 'Speckled Cherry' or 'Speckled Cross' with a variety of logos, colours (e.g. white, pink, green and blue) and shapes (EMCDDA and Europol, 2014).

Both the tablets' and powder composition can be considerably different from a product to a product as they may contain 4,4'-DMAR alone or in combination with other psychoactive substances, including: synthetic cathinones, synthetic cannabinoids, benzofurans and ethylphenidate. **To date, the purity of the 4,4′-DMAR available on the drug market has not been reported (EMCDDA, 2015).**

As described by the EMCDDA (2015), seizures of products containing 4,4′-DMAR were reported in seven Member States (Denmark, Finland, Hungary, the Netherlands, Romania, Sweden and the United Kingdom), with a preferential availability of this substance in the Hungarian drug market.

In some cases, 4,4′-DMAR is offered on the illicit market as 'ecstasy' and 'amphetamine', therefore users may not always be aware of the associated health risks (EMCDDA, 2015).

Because of serious adverse effects reported, including fatal intoxications entirely caused by (±)-cis-4,4'-DMAR, this drug was banned in the UK, being placed in schedule 1 (ACMD, 2014) of the Misuse of Drugs Act 1971.

4,4'-DMAR is also under drug control legislation in Bulgaria; Croatia; Cyprus; Czech Republic; Denmark; Estonia; Finland; Germany; Hungary; Ireland; Lithuania; Luxembourg; Netherland; Norway; Poland; Slovenia; Spain; Sweden, Turkey, Japan (EMCDDA 2015, ELDD 2016). **Additionally, in March 2016, the commission on Narcotic drugs decided to internationally control 4,4'-DMAR adding it into schedule 2 of the Convention on Psychotropic Substances of 1971. The decision became effective in November 2016 (UNODC, 2016).**

Pharmacology

(±)Cis-4,4′-DMAR is a monoamine-releasing agent that displays high potency at all three monoamine transporters. According to some pharmacodynamics studies, this compound was found to show equivalent potency at the dopamine and norepinephrine transporters (DAT and NET, respectively) and greater potency at the serotonin transporter (SERT), in

comparison with d-amphetamine and aminorex (Brandt et al., 2014a).

In another study performed on rat brain synaptosomes, the monoamine releasing activity of (±)cis-4,4'-DMAR and (±)trans-4,4'-DMAR isomers was compared to that of MDMA. Both cis-4,4'-DMAR and trans-4,4'-DMAR were found to be stronger than MDMA as releasing agents at the DAT and NET. Concerning the activity at SERT, (±)cis-4,4'-DMAR acted as a fully effective releasing agent, whereas (±)trans-4,4'-DMAR acted as a fully efficacious uptake blocker (McLaughlin et al., 2014).

Additionally, our unpublished data obtained using PreADMET online server (https://preadmet.bmdrc.kr/) indicate that 4,4'-DMAR has similar predicted blood brain barrier (BBB) permeability as MDMA.

To date, no published data are available on the pharmacokinetics of 4,4′-DMAR in animals or humans and no metabolites of this substance have been detected up to now (EMCDDA, 2015).

Fatalities and adverse effects

In December 2012, 4,4′-DMAR was first detected in fatalities reported from Sweden, followed by Denmark, Finland, Hungary, Romania, Sweden, France and the United Kingdom (EMCDDA, 2015).

Since October 2013, 38 4,4'-DMAR-related deaths have been identified in the United Kingdom (e.g. 36 in Northern Ireland 1 in Scoltand and 1 in England); 8 in Hungary; and 1 in Poland in July 2013 (ACMD, 2014, Cosbey et al., 2014; EMCDDA, 2015; Shropshire Star, 2016)

In all 47 cases, the 4,4'-DMAR presence, either alone or in combination with remaining recreational drugs (e.g. cocaine, amphetamines, cannabis, benzodiazepines, antidepressants, second-generation antipsychotics, opioids and synthetic cathinones), was confirmed at post-mortem (ACMD, 2014, EMCDDA, 2015).

Conversely, non-fatal 4,4'-DMAR acute toxicity events are characterized by features such as: hyperthermia, pupil dilation, muscular spasm, seizures, increased perspiration, cardiac and respiratory arrest, agitation, confusion, convulsions, unconsciousness and paranoid features. The presence of and/or interaction with other substances may account for some of the reported effects (EMCDDA and Europol, 2014; EMCDDA, 2015).

The 4,4′-DMAR activity on catecholamine transporters may be relevant in this respect, especially if the molecule is associated with recreational drugs altering dopamine and norepinephrine levels.

Indeed, psychotic episodes can occur if 4,4'-DMAR is ingested in combination with other catecholamine-releasing agents (e.g. amphetamine-type stimulants, cocaine) and cardiovascular issues may result from the excessive systemic levels of norepinephrine released.

Additionally, the risk of experiencing a serotonergic syndrome may be increased by the association of 4,4'-DMAR with compounds affecting either the serotonin release (e.g. MDMA/ecstasy) or its reuptake, such as the selective serotonin reuptake inhibitors (SSRIs) (McLaughlin et al., 2014).

We aimed here at reviewing the literature relating to 4,4'-DMAR intake. Furthermore, we aimed at describing, through an assessment of related anecdotal online reports, a range of clinical pharmacological issues to its misusing issues potential.

Methods

To identify peer-reviewed papers and online reports commenting on 4,4'-DMAR misuse issues, a comprehensive search on the Embase, Scopus; Google Scholar and Pubmed/Medline databases was performed using the following key words: (4,4'-DMAR) AND (*abuse* OR *misuse* OR *poisoning* OR *dependence* OR *addiction*). No language or time restrictions were placed on the electronic search; focus was on both pre-clinical and clinical data and covered the period up to November 15th, 2016.

To identify information on 4,4'-DMAR misusers' first-hand experiences, a qualitative/observational, i.e. netnographic, approach on selected websites was carried out. In doing so, between March and October 2016, a range of qualitative Google searches was carried out, in English, using key words such as '4,4'-DMAR and abuse', '4,4'-DMAR and misuse'; '4,4'-DMAR and experience'; 'Serotoni and forum'; 'Speckled Cherry forum'; 'Speckled Cross forum'; 'Para-Methyl-4-Methylaminorex forum'; '4-methyl-euphoria forum'; '4-methyl-U4Eu forum'; '4,4-dimethylaminorex forum'.

The first 2 pages/20 hits per keyword (e.g. 60 per language; 120 links) were considered. A number of websites were subsequently excluded, because: not relevant; being duplicates; or requiring a registration/payment procedure.

A total of six sites hosting forum activity around 4,4'-DMAR use were identified:

1. https://www.chemsrus.com;
2. https://www.reddit.com;
3. https://www.ukchemicalresearch.org;
4. http://www.bluelight.org;
5. http://www.psychonaut.com/forum.php;
6. https://drugs-forum.com.

Overall, twenty detailed posts (19 in English, and 1 in French) focusing on 4,4'-DMAR use were found and individually analysed by identifying the common topics and patterns of discussion. Conversely, a range of fora posts/threads relating to a few 4,4'-DMAR themes, including:

1. routes of administration and doses
2. desired effects
3. adverse effects
4. comparisons with other substances
5. concurrent intake with other drugs
6. medication use to counteract 4,4'-DMAR action
7. overall impression
8. availability of harm reduction messages; warning other people regarding possible drug-related health risks

were specifically analysed. No posts/other contributions to fora discussions were made, and no information or clarification of content was sought by the researchers.

Ethical consideration

Our research involved the collection and characterization of already existing reports published on public Internet fora. A discrete approach was undertaken, and no interactions with fora members were made. In order to preserve the anonymity of the

fora members, users' nicknames were not mentioned and the quotes were not integrally reported. Ethics' approval for the study was granted by the University of Hertfordshire School of Pharmacy Ethics Committee, on December 15th, 2010 (reference code PHAEC/10-42), with a further 5-year extension of the approval having been granted in November 2013.

Results

Literature identification and analysis

The comprehensive literature search led to the identification of 13 peer-reviewed papers and 3 reports (EMCDDA and Europol, 2014; ACMD, 2014; EMCDDA, 2015) focusing on 4,4'-DMAR use, which were critically analysed.

Published information on routes of administration (ROA), suggest that nasal insufflation and oral consumption practices are the most widely used followed by inhalation and injection (ACMD, 2014; EMCDDA and Europol, 2014; EMCDDA, 2015; Cosbey et al., 2014; Coppola et al., 2015; Glanville et al., 2015; Hentig, 2016).

Oral doses were described ranging from 10 to 200 mg, while the insufflated ones vary from 10 to 65 mg (ACMD, 2014; EMCDDA and Europol, 2014; EMCDDA, 2015; Coppola et al., 2015; Glanville et al., 2015; Nizar et al., 2015; Hentig, 2016).

Oral consumption was reported to be commonly practiced by directly ingesting tablets/powder or by swallowing powder

previously wrapped in cigarette papers ('bombing') (ACMD, 2014; EMCDDA and Europol, 2014; EMCDDA, 2015; Cosbey et al., 2014; Coppola et al., 2015; Glanville et al., 2015).

Commonly reported desired effects include: euphoria, increased sociability and energy, alertness, and increased confidence; while untoward effects vary from increased heart rate, hyperthermia, sweating, agitation, jaw clenching (bruxism), facial spasms, stimulation, nausea, dysphoria, dilated pupils, to psychosis and hallucinations (ACMD, 2014; EMCDDA and Europol, 2014; EMCDDA, 2015; Cosbey et al., 2014; Coppola et al., 2015; Glanville et al., 2015).

The use of a range of sedatives and anxiolytics was reported as a common practice to reverse 4,4'-DMAR long-lasting stimulants' effects (12-16 hours) (Glanville et al., 2015; Schifano et al., 2016).

Desired and untoward effects were described to be comparable to those observed with other stimulant-type drugs (e.g. MDMA, mephedrone) characterized by similar pharmacology and pharmacokinetic properties (Brandt et al., 2014a; McLaughlin et al., 2014; Schifano et al., 2015, 2016; Nils et al., 2016; Hentig, 2016; Lucchetti et al., 2016).

Combination with other drugs (e.g. synthetic cathinones, amphetamines, cocaine) has been widely reported and accounted for several toxicity events (e.g. cardiovascular effects, psychotic symptoms, agitation hyperthermia) and

fatalities (Brandt et al., 2014b; ACMD, 2014; EMCDDA and Europol, 2014; EMCDDA, 2015; Cosbey et al., 2014; Coppola et al., 2015; Glanville et al., 2015; Berg, 2016; Hentig, 2016). Social cohesion, support, and harm reduction advice have been also widely described among a range of NPS users (Soussan & Kjellgren, 2014).

Self-reported routes of administration and dosages

Dosages and routes of administration were found to be a widely-debated topic of discussion. Overall users tended to specify doses, frequency of re-dosing and the combination of different ROA to achieve the optimal 'high level'. The indication of dosages and ROAs was reported by 85% (17/20) of users. Among them, 76% (13/17) described oral use, 12% (2/17) reported the intranasal ROA or vaping, 12% (2/17) reported a multiple re-dosing practice describing an oral ingestion followed by the intranasal route, or by snorting and vaping. The formulations described were powder and pellets. The oral doses ranged from 10 to 120 mg; the intranasal ones varied from 25 to 30 mg and the vaporised doses were in the 10-60 mg range **(Figure 2).** A quarter of users (5/20) described a slow onset of the drug's psychoactive effects **(Figure 2)**.

Self-reported desired and untoward effects

Intensity and duration of the 'positive' effects were widely reported; 70% (14/20) of users described a range of positive effects including: stimulation, energy increase, euphoria,

relaxation, increased sociability, empathy, disinhibition, arousal **(Figure 2).**

By contrast, a range of adverse effects was described by 55% of users (11/20) and included: hallucinations, altered perceptions, insomnia, queasiness, jaw clenching/tension/bruxism, blurry vision, nystagmus, psychosis, confusion, nausea, sweatiness, increased heart rate, and hyperthermia **(Figure 3)**.

The effects of 4,4'-DMAR were compared with those associated with other stimulant (e.g. 4FA, MDMA, 6-APB, APB, 3-MMC, 4-MMC, MDPV a-PVP, 4-MMA, MDMA) intake by 50% of the users (10/20). Comments included: *"Way better than cathinones!…it was also way way better than 4-FA which never really felt serotonergic to me";…"It definitely felt stronger than any of my experiences on 6-APB though";…"I found it to be a very nice experience, somewhat comparable to 3-MMC but a lot longer lasting and thus with a lot less craving")* **(Figure 3).**

Association with other recreational drugs

Some 30% (6/20) of users used 4,4'-DMAR with other drugs, especially alcohol (66%; 4/6); 6-APB (17%; 1/6); and phenylpiracetam (17%, 1/6) **(Figure 3)**.

Some users described a potentiation of 4,4'-DMAR effects whilst on alcohol *("definitely potentiated with alcohol"*); and a feeling of "head clearness" ("*Normally I would become sloppy and hazy with alcohol, but this was clear and fresh"*). Finally,

to cope with social anxiety issues, 4,4'-DMAR was associated with either alcohol or 6-APB.

Medication(s) self-administered to revert 4,4'-DMAR action

Since 4,4'-DMAR stimulant effects seemed to be quite long-lasting, some 20% of users (4/20) stated they had used sedatives/anxiolytics (e.g. diazepam, zolpidem, trazodone, baclofen, flubromazepam, and etizolam) **(Figure 3)**.

Overall impression

Some 50% (10/20) of fora users provided their peers with either a positive or a negative summary of their 4,4'-DMAR personal experiences, hence to promote or denigrate the use of this drug **(Figure 4)**. Indeed, most of them described their experience as *"awesome", "enjoyable", "nice", "clean", "comfortable"* while others considered it *"disappointing"*. Other users described their experience using technical language which involved a reference to the molecule's pharmacodynamics *("I really liked the dopamine-serotonin activation ration"*); pharmacokinetics ("…a *biphasic effect with a stimulation predominant on the side end…residual stimulation the day after"*); or addictive liability levels ("*significative addictive potential"*).

Overall, some users appeared enthusiastic *("I think it's the most beautiful, awesome stimulant I've ever tried"…"to me this feels like a product the market has been seriously lacking for a long time"*).

Harm reduction advice

Some fora discussions identified here were characterized by a general concern for safety, with some 30% (6/20) of users providing a range of advice, including: avoiding concurrent ingestion of other drugs both on the intake day and for a few days after 4,4'-DMAR use*;* being careful about both the dosage self-administered and tendency to re-dosing, whilst considering the 4,4'-DMAR intensity of the psychoactive effects *("this is not a functional/nootropic stimulant, this is a more potent version of MDMA/APB")* (**Figure 4**).

Discussion

4,4'-DMAR popularity in a range of different countries may well be related to both its significant psychoactive effects and the current intense web-based marketing activities (EMCDDA and EUROPOL, 2014).

This drug belongs to the category of NPS which includes numerous harmful substances like: "Synthetic Cannabinoids" (the largest group of new drugs monitored by the EMCDDA and found to be highly toxic according to the high affinity and efficacy at the level of the neural CB1 receptors) (EMCDDA, 2016; Santacroce et al., 2015; De Luca et al., 2015); "Synthetic Cathinones" (the second widest group monitored by the EMCDDA, implicated in a number of overdose deaths and serious sympathomimetic adverse effects) (EMCDDA, 2016);

"hallucinogens" (including compounds like 25I- and 25C-NBoMe, responsible for acute and chronic toxicities, according to their ability to act at the level of the serotoninergic system) (Bersani et al., 2014).

The public health risks related to 4,4′-DMAR use may be associated with a range of factors, including: drug availability; quality and purity; levels of risk awareness amongst users; and potential combination of this drug with other substances (e.g. entactogens, stimulants and/or depressants including alcohol) (EMCDDA, 2015; EMCDDA and Europol, 2014).

Much of our knowledge about 4,4'-DMAR comes from retrospective self-reports from recreational users (e.g. the 'e-psychonauts', Orsolini et al., 2015) who use the fora as a widely available platforms to disseminate a range of drug-related personal experiences.

According to previous reports (ACMD, 2014; EMCDDA and Europol, 2014), the main 4,4'-DMAR routes of administration include oral ingestion, at a dosage of 10-200 mg per occasion, and nasal insufflation (10-65 mg dosage), with injection having been only rarely reported.

In the present study, fora users have been widely sharing their 4,4'-DMAR intake experiences and knowledge, with most (80%) messages having been posted in 2013, e.g. in parallel with first seizures of the drug in the EU. **Starting from 2015, the online discussions focusing on this drug, rapidly**

disappeared from the surface web, in parallel with 4,4'-DMAR being banned in different countries.

This tendency was already observed with other substances, such as 2C-T-7, a stimulant drug which rapidly disappeared from the cyber market after control legislation (Schifano et al., 2005). However, this does not excluded the possibility of a move of 4,4'-DMAR-related illegal activities into the 'deep web', as already observed with other controlled substances (Orsolini et al., 2015). Moreover, the fall noted in deaths involving this molecule in 2015 (Corkery, 2016) may be due, in part, to the control of this substance. Equally, the fall may be due to fewer individuals using it following the bad reputation it received because of the sudden outbreaks of these severe adverse effects. Overall, fora users mostly ingested 4,4'-DMAR powder and pellets, at dosages (e.g. 10-120 mg) consistent with previous reports (ACMD, 2014; EMCDDA and Europol, 2014), although vaping and snorting ROAs were at times preferred, with multiple re-dosing practice being described as quite a popular approach.

Most of the 4,4'-DMAR fora enthusiasts described here seemed to present with a previous history of drug misuse, whilst possessing large levels of technical/pharmacological knowledge regarding NPS and 4,4'-DMAR in particular, hence

well resembling the classical/standard 'e-psychonauts' description.

The present report seems to confirm that 4,4'-DMAR is a popular recreational drug which, similarly to remaining stimulants, is associated with feelings of stimulation, euphoria, energy, alertness, increasing confidence. The powerful 'pro-social' effects (e.g. increased empathy, feelings of friendliness, interpersonal closeness, openness) were here particularly emphasized (EMCDDA and Europol, 2014). Related stimulant effects seemed to be characterized by a significant lag time, peaking in 2-5 hours, but were long-lasting (e.g. 12-16 hours) as well (Glanville et al., 2015).

Consistent with previous studies (Glanville et al., 2015), untoward effects were here described in some 55% of users, starting from the minimal (e.g. 5mg) dosage, and included: nausea, dysphoria, agitation, confusion, aggression, sweating, increased heart rate, hyperthermia, dilated pupils, psychosis, hallucinations, insomnia, jaw clench/jaw tension/bruxism, blurry vision, nystagmus.

Both the psychoactive (including the entactogenic and nootropic properties) and the adverse effects being here described are consistent with 4,4'-DMAR being a phenethylamine/MDMA like compound (Bershad et al., 2016; Schifano et al., 2016; Iversen, 2013; Miliano et al., 2016).

The 4,4'-DMAR pharmacodynamics profile may be broadly similar to that of other stimulants. However, because of both the intensity and the long-duration of its effects, the 4,4'-DMAR intake may be a reason of particular concern, and especially so if the molecule, as here described by 30% of users, is ingested in combination with remaining serotonergic/dopaminergic compounds (Coppola et al., 2014).

These peculiar clinical pharmacological characteristics may help explaining the disturbingly high rate of 4,4'-DMAR fatalities observed over a relatively short period of time in the EU and especially in Northern Ireland (EMCDDA and Europol, 2014).

To counteract the long-lasting stimulant effects, it is of interest to note that some 20% of users here allegedly self-administered with a range of sedatives, including designer/'exotic' benzodiazepines (Schifano et al., 2016). In this way, users were arguably adding further health risks to the already risky practice of ingesting a powerful, but virtually unknown to the medical literature, stimulant such as 4,4'-DMAR.

Limitations

There are a number of possible limitations of the present study; a multi-lingual analysis of a larger sample of websites could have provided better levels of information. Furthermore, only publicly available web sites/fora were monitored here, and

further data of interest could possibly have been identified by the analysis of the 'deep web' and 'dark net' material (Orsolini et al., 2015). We made no 4,4'-DMAR purchase attempts, hence one could argue about the product content/dosage being delivered. Overall, anecdotal reports are only partially reliable and it may be inappropriate to trust information obtained from the internet without independent verification. Additionally, there is no certainty that multiple threads or posts were generated by different individuals, as it is not unusual that people can access the fora multiple times with different pseudonyms.

Since very few peer-reviewed papers relating to 4,4'-DMAR misuse issues were identified, the present conclusions mainly relied on sources (e.g. web sites) are characterized by levels of unreliability. Only large-scale, adequately controlled, clinical studies can give a clear indication of a drug characteristics and adverse effects. However, in line with present observations, previous studies (Corkery et al., in press) Schifano et al., 2010; Soussan & Kjellgren, 2014; https://www.drugabuse.gov/publications/drugfacts/nationwide-trends) have clearly suggested that the increase in online trafficking/debate about a specific psychoactive drug typically precedes the occurrence of clinical incidents at the population level.

Conclusions

This study suggests that fora members co-operate in exchanging an extensive body of knowledge about NPS, including 4,4'-DMAR. The combination of sensation seeking, harm-reduction, and social networks' pressure may arguably have detrimental effects on many aspects of fora members' drug intake behaviour. The issue of 4,4'-DMAR misuse may be a reason for concern; consumers may not be fully aware of the pharmacological activity, and possible medical consequences, of the compound(s) they are ingesting. Indeed, 4,4'-DMAR misuse may often occur in the context of polydrug intake, and the pharmacodynamics/pharmacokinetics' interactions of 4,4'-DMAR with other substances are not known.

Further analyses should be undertaken to better draft a risk profile for this drug. As with any centrally active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of any products', including 4,4'-DMAR, misuse. Additionally, prevention strategies should be developed and better public awareness levels should be promoted.

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Figure 1: 4,4'-DMAR chemical structure

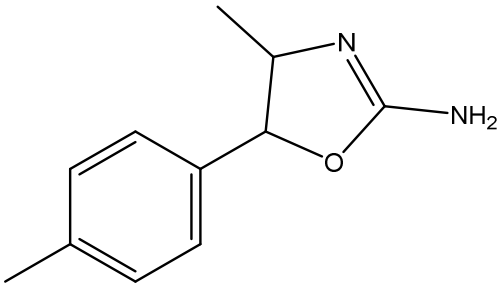

Figure 2: 4,4'DMAR self-reported routes of administration and dosages; long onset awareness; self-reported desired effects

ROAs				Long onset awareness
Oral	Intranasal	Vaping	Multiple ROA	*"I know this stuff is a slow burner so will stay patient"*
"60mg serotoni in a decaffeinated"	*"I did 30mg powder up the nose"*	*"60mg is a good dose with *good* 4,4'-DMAR... vaporising the stuff has a very pleasant rush"*	*"I dosed 30mg orally... I dosed another 30mg orally after 2 hours...after 6 hours I make the decision to re-up one more time 30mg, 5mg oral plus 25mg intranasal*	*"Long come up 80 minutes at least, very strong serotonergic effects after 2,5 hours"*
				"I took two due to the long come-up"
				"Come up was a little rough"
				"I took two pellets (60 mg each) due to the long come-up"
"As for dosing, I've tested once thus far, found ~25 orally to be fantastic"			*"10 mg orally, 20 snorted + 10 vaporized"*	**Self-reported desired effects**
				"My pupils were huge... Meanwhile I was feeling damn good"
"1 tablet (60 written on the back of a pink/orange hexagonal pill, assumed dosage of 60mg) taken with water"				*"I noticed some pleasant stimulation...energy increase, mood lift... Subtle, but there... The euphoria feels more energetic. Increasingly good mood and feel like talking to everyone...a full fledged empathogen experience that show no signs of stopping.... There's not that super pushy loved up need to touch and hug and express empathy towards everyone"*
"90mg in a coffee"				*"Feeling stimulated, happy and full of energy but not especially 'high'... some euphoria like a couple of beers... feeling slightly wonky/euphoric... Feels like the effects are still subtly building"*
"60 mg is almost too much for me "				*"I felt just generally happier"*
"I started with 32 mg and redosed 3x 20 mg lines over the course of 3 hours, so a total of 90 mg"				*"Slight elevation of mood noted. ..Arousal was noted, and all anxiety was not only reduced but totally removed...Having a conversation with someone who I normally get anxious around, but I'm beaming, finding it stunningly easy to convers... Arousal was noted, and all anxiety was not only reduced but totally removed... I feel witty and seem to be getting a couple of laugh... shining mood"*
"Take 1 pellet (60mg)"				*"I still wasn't feeling 'high' but probably a bit more happy euphoric than normal"... I was perhaps more animated than normal excited"*
"I took two pellets (60 mg each) due to the long come-up"				*"Amazing euphoria indeed - makes the act of just breathing so much clearer and transparent...the highly bodily euphoria multiplies... Touchy feely, enjoying running my hands through my hair... There's still a general feeling of euphoric well-being lingering"*
"I found 90-95mg single dose (with no redosing) to be my sweet spot. 60mg was underwhelming and 120mg (and higher) was just over the top"				*"Definite waves of euphoria that very familiar sort of peaking wave feeling"*
"50-60 mg is all you need for a fun time "				*"Perfect for socialising, I' m chatty, and clear headed...euphoric without being overwhelming...Feeling pretty damn...Chatty euphoric and feeling really nice, no body load no tension no horrible over stimmed feeling at all...completely sociable"*
"Took an hexagonal pellet labelled "ST 60" containing 60 mg of 4,4-DMAR "				*"Higher than baseline for at least two days post-party"*
"I decided to ingest 5mg of 4,4'-DMAR by dissolving it in tea and drinking the mix"				*"This has amazing euphoria, mood lift and an incredible body high"*
"Retested at 70 mg (orally), the dose response curve is really-really-exponential"				*"I was brought into a nice relaxed state, felt very little stimulation"*
				"It starts to get really nice... I feel very good, very "MD-like" but with a clarity of feeling in the head, which is not usual (normally I feel really bashed the contrary)... I converse deeply with people, alternating intellectual discussion and emotional discussion...music is orgasmic... I understand better the effect of light in the head...intellectual debate... very euphoric"
				"Had waves of euphoria (the feeling that your eyes wanna roll back into your head if u know what I mean) and a generally good mood "

Figure 3: 4,4'-DMAR self-reported untoward effects; self-reported comparisons with other substances; self-reported association with other drugs; self-reported medications use to revert 4,4'-DMAR action.

Self-reported untoward effects
"The most prominent hallucination was things like light switches and door knobs slowly sliding down the wall or door to the floor...Or sometimes they might move in a circular motion. Mild heightening of colour was noted as well... Around bedtime when they wanted me to sleep and turned out the lights and this I began to have some pretty strong psychosis"
" Blurry vision, a hint of nystagmus... pupils definitely dilated... thoughts are getting more cloudy"
"Feeling a bit queasy, bit of jaw clench"
"On the way to a party, I'd swear my vision has become somewhat blurred, but only by the smallest margin, it's dismissed...the more I focus the more I realise it's still somewhat affected"
"Queasy nauseous feeling... I seem to be stumbling over my words slightly... feeling maybe a bit fuzzy-headed...notice I'm a bit unsteady on my feet... Listening to my notes now I was rambling a little but wasn't feeling intoxicated..., feeling slightly wonky...possibly some very slight jaw tension"
"Bruxism - if I had to interact socially, people would probably notice stereotypical tongue movements"
"My pupils are also still dilated"
"Feeling a bit sicky but only ever so slightly... Quite flushed face... The lack of pupil dilation is particularly appealing as its something that tends to make me incredibly paranoid... being pretty hostile... very warm slightly sweaty...Pretty mashed. Spent the night in a bath tub in love with everything. Pupils almost the same size as my irises"
"I'm sweating a little... Heart rate and BP are only slightly elevated"
"I sweat profusely, drink lots of water, almost no alcohol. I measure my pulse: 90"
"At this dosage, serotoninergic signs appear: hyperthermia with sweating. No tachycardia"

Self-reported association with other drugs
"Normally I would become sloppy and hazy with alcohol, but this was clear and fresh"
"I still wasn't feeling 'high' but probably a bit more happy euphoric than normal...went on to drink 4 pints of beer through the evening.... I was perhaps more animated than normal excited but sometimes alcohol itself has that effect on me"
"Ingested 40 mg of phenylpiracetam in conjunction with dropping the 60 mg tablet"
"Decide to have a beer as it's a lovely sunny evening and the sickness has passed . The alcohol seems to have kicked the peak back in ...definitely potentiated with alcohol... Also being able to drink is a huge winner"
"I managed to get my hands on the drug yesterday, and tried at the end of a 130mg 6-APB comedown"
"The alcohol begins to flow freely but stay on the same beer for 1 hour afraid to react badly with this substance. I might have had to stay alcohol eventually"

Self-reported comparisons with other substances
"Way better than cathinones!...it was also way way better than 4 FA which never really felt serotonergic to me"
"Pupils definitely dilated (similar to MDMA/6-APB levels)... ...It definitely felt stronger than any of my experiences on 6-APB though...The next day and the infamous suicide Tuesday effects following some MDMA of my recent rolls never came. I was perfectly fine. No hangover even... I would have to say that I'd rate this substance above MDMA and even 6-APB (my previously favorite empathogen)... This is a more potent version of MDMA/APB... It definitely felt stronger than any of my experiences on 6-APB though"
"I'd sooner stick to APBs for my kicks"
"Feeling normal head-wise but notice I'm a bit unsteady on my feet, like a 6-APB come up or a couple of drinks without the headspace"
"I found it to be a very nice experience, somewhat comparable to 3-MMC but a lot longer lasting and thus with a lot less craving"
"I quite am enjoying smoking, on APB or any similar chems very rarely manage to smoke at the peak or for some hours after... Feel fully functional not mashed like with APB"
"I can say it's nice, reminds me of 4-MMC but more mentally stimulating, less physically stimulating"
"To me 4,4'-DMAR feels a lot like a more sedating less stimulating version of Mephedrone (4-MMC). It actually felt closer to 4-MMC than certain other drugs that are structurally closer, like 3-MMC... and the duration is also incredibly short, plus I'd prefer a more dopaminergic stim to vape anyway like MDPV or a-PVP... I had my little stint with it over the course of one morning but don't plan to lay hands on it again, that risk is just too big if it does turn out to be like 4-MMA pharmacologically"
"I felt opposed to odd occasions while on 6-APB where I've felt the urge to take 'just one more' despite knowing the trip's ending soon"
"It has empathogenic unique qualities, and although there is a significant stimulus side, it can be compared to APB...It starts to get really nice as any, I feel very good, very 'MDMA-like' "

Self-reported medications use to revert 4,4'-DMAR action
"I was able to eventually get some sleep with the help of 10mg valium, 20mg zolpidem, and 150mg of trazodone...Would I do 4,4 Dimethylaminorex again"
"Before I got on the flight took 100mg baclofen ...the baclofen was in the background providing some background anti-anxiety effects"
"Lingering stimulation was helped with 3 mg of Flubromazepam 2 hours before bedtime"
"It's been 6 hour since the last line and I cannot sleep despite 2 mg Etizolam and a lot of weed... The duration seems to be incredibly long"

Figure 4: Self-reported overall impression; harm reduction advice

Overall impression	Harm reduction advice
"I think it's the most beautiful, cleanest feeling, awesome stimulant that I have tried"	*"Just heed all warnings about avoiding use of other drugs for the next day or 2. And in case you didn't pick up the moral of the story: this is NOT a functional/nootropic stimulant. This is a more potent version of 'MDMA/APB' "*
"Overall this was enjoyable but would need to be a lot stronger to retain my interest, I'll try a higher dose next time but at this level of effects, I'd sooner stick to APBs for my kicks"	*"My advice would be to not take two pellets"*
"So, in summary, this experiment was disappointing, more so than last week's with 60mg"	*"New users, I'd recommend starting lower (30mg~) and then redosing if necessary"*
"At 60 mg, this was a more powerful drug than I had expected"	
"I really liked the dopamine-serotonin activation ration. For me it was mostly dopaminergic but with noticeable and nice serotonergic effects ...Very worthwhile compound"	*"I don't think it's necessarily super dangerous to try if you stick to a low dose and make sure to combine it with nothing... I wouldn't go much higher even if your stuff seems weak, no sense in putting yourself in unnecessary harms way... Anyway that's all fine if you just want to try it to see what it's like, but considering the close relationship to 4-MMA, and the likelihood that it's a potent neurotoxin at dosages we don't yet know, with possible severe side effects with regular use, I wouldn't make plans to try it more than once"*
"This is euphoric but not like a hard kick... it's gentle and comfortable but at the same time very very nice ... it's clean... To me this feels like a product the market has been seriously lacking for a long time ... I'd really urge stim people to give it a whirl for a sociable functional stimulation...if you research this with an open mind then I really don't think you will be disappointed for me its just what I have been looking for ...makes you feel sociable without paranoia and a damn nice euphoric lift"	
"Less mongy than I was expecting, quite stimulating...Vaping on the peak resulted in a rush stronger than MDMA but the rush itself was short-lived and then faded back into additional stimulation... Think this stuff is worthwhile"	*"I guard against this by measuring out a suitable amount/number of doses beforehand"*
"Any euphoria might be had at high levels is easier (and safer) obtained by other compounds"	*"It is dangerous: a great desire to redose... life-threatening interactions"*
"Molecule with a unique high indeed but very close to the md in the first part, a truly amazing kinetic, no "rush" but no "down", a biphasic effect with a stimulation predominant on the side end.. a residual stimulation the day after...very nice but very long (almost half of the effect) and then a significant addictive potential"	
"Overall I regret my decision of even taking it. To all other people willing to try it- I would say start with 5mg than double... as there was no real effect"	