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Performance and Image Enhancing Drugs: the abuse of cognitive enhancer Piracetam

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Running Title: Piracetam misuse: a review of online reports

Abstract

Introduction: *Performance and Image Enhancing Drugs (PIED), also known as “lifestyle drugs”, are increasingly sold on the Internet to enhance cognitive as well as sexual, muscular, attentive and other natural capacities. Our analysis focus on the misuse of the cognitive enhancer Piracetam.*

Methods: *A literature review was carried out in PsychInfo and Pubmed database. Considering the absence of peer-reviewed data, additional sources of unstructured information from the Internet was carried out between February 2012 and July 2013. Additional searches were conducted using the Global Public Health Intelligence Network (GIPHIN), a secure Internet-based early warning system developed by Health Canada and the World Health Organization (WHO), which monitors media reports in six languages, Arabic, Chinese, English, French, Russian and Spanish.*

Results: *Piracetam is sold via illicit online pharmacies with no need of prescription at low prices. Buyers, mainly healthy individuals, purchase the product to enhance study and work-related performances as well as for recreational purposes. Its non-medical use is often associated with the occurrence of side effects such as hallucinations, psychomotor agitation, dysphoria, tiredness, dizziness, memory loss, headache and severe diarrhea; moreover, several users declared to not have felt any cognitive improvement nor psychedelic effects.*

Conclusions: *This is a new and fast growing trend of abuse that needs to be extensively monitored and studied also by using near real-time and unstructured sources of information such as Internet news and online reports in order to acquire rapid knowledge and understanding. Products sold online might be counterfeits and this enhances the health risks.*

Key Words: Piracetam, Performance and Image Enhancing Drugs, Addiction, Drug Abuse, Cognitive Enhancer, Online Pharmacies.

1. INTRODUCTION

In recent years, a rapidly spreading of substances known as ‘Performance and Image Enhancing Drugs’ (PIED), also known as ‘lifestyle drugs’, has been recorded (Evans-Brown, McVeigh, Perkins, & Bellis, 2012). PIEDs are mainly sold online, via illicit online pharmacies, as the most immediate way to enhance cognitive, sexual, muscular, attentive and other natural capacities, even if their level of safety, composition and legal status are mostly unknown (European Monitoring Centre for Drugs and Drug Addiction [EMCDDA], 2010; EMCDDA, 2011; Advisory Council on the Misuse of Drugs [ACMD], 2011; Corazza, et al., 2011; Schifano, et al., 2006; Larance, Degenhardt, Copeland, & Dillon, 2008). These also include pharmaceutical products, which can be bought without a prescription and at discounted prices, such as Pregabalin and Adderall (Orizio, et al., 2009; Littlejohn, Baldacchino, Schifano, & Deluca, 2005).

In particular, this article will focus on Piracetam, a cognitive enhancer, which has been abused by healthy individuals to enhance their functions in study and work-related performances (Schifano, et al., 2003; Corazza, et al., 2013).

Piracetam is a cyclic derivative of the neurotransmitter γ -aminobutyric acid (GABA), originally marketed in 1971 by UCB Pharma. It was the first ‘nootropic’ drug (Giurgea, 1972), an agent that acts on cognitive function without causing sedation or stimulation (Winblad, 2005). It was found originally to be effective as a protective agent in hypoxia-induced amnesia.

Although piracetam is a derivative of GABA, its mechanism of action appears to be unrelated to the properties of this neurotransmitter. Piracetam affects a number of neuronal proteins; some evidence suggests that piracetam can act at the α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor as an allosteric modulator binding in six different positions (Ahmed & Oswald, 2010) and that it may have an effect on NMDA glutamate receptors (Cohen & Müller, 1993). However, while the exact mode of action of piracetam is a matter of debate, there is increasing evidence that its underlying effect is to restore cell membrane fluidity (Fassoulaki, Kostopanagiotou, Kaniaris, & Varonos, 1985; Peuvot, Schank, Deleers, & Brasseur, 1995).

Restored membrane fluidity induced by Piracetam may have a number of physiological consequences including restored neurotransmission (Winblad, 2005), increased oxygen consumption in the brain (Jordaan, Oliver, Dormehl, & Hugo, 1996), enhanced neuroplasticity (Brandao, et al., 1996), neuroprotection (Brandao, Paula-Barbosa, & Cadete-Leite, 1995) and anticonvulsant action (Benesova, 1980).

Consistent with its varied pharmacological effects, Piracetam has documented benefit in a diverse range of indications. The largest amount of data is about the therapeutics use of Piracetam to treat early Alzheimer's disease and age-associated memory impairment (Waegemans, et al., 2002); a large meta-analysis of all available clinical studies provided compelling evidence for the global efficacy of piracetam in a diverse group of older subjects with cognitive impairment (Waegemans, et al., 2002). This proposal was later supported by observations that piracetam specifically enhances membrane fluidity in aged brain material, showing no effect in membranes from young brains (Müller, et al., 1997).

In addition to Alzheimer's disease and age-associated memory impairment, Piracetam showed good clinical outcomes in the treatment of a range of neuropsychiatric disorders including vertigo, cortical myoclonus, dyslexia, neuropathic pain and tardive dyskinesia (Winblad, 2005; Danilova Grafova, & Reshetniak, 1996; Libov, et al., 2007).

Piracetam doses usually range between 2.4 g/die and 8 g/die, even if in the treatment of cortical myoclonus it can be administered at higher dosages (up to 24 g/die) (Winblad, 2005).

In this context, the present study aims to identify and investigate the non-medical use of Piracetam, while collecting unprecedented information on its psychoactive effects.

2. MATERIALS AND METHODS

The literature on Piracetam misuse was searched in PsychInfo and Pubmed databases. Considering the absence of peer-reviewed data on its misuse, results were integrated with a multilingual qualitative assessment of a range of websites, drug fora and other online resources (i.e.:

newsgroups, chatrooms, mailing lists, e-newsletters, bulletin boards and videos). Between February 2012 and July 2013, exploratory qualitative searches of 227 websites have been carried out in English using generic and specific keywords, such as “legal highs”, “research chemicals”, “online pharmacy”, “piracetam”, and “nootropil” in the Google search engine. These websites were monitored on a regular basis, daily (n=32), weekly (n=168) or monthly (n=27) depending on relevance. Links from forums, websites and other related material, including newspapers and magazines, were followed as well. Additional searches were carried out in the database provided by the Global Public Health Intelligence Network (GPHIN). This is a secure Internet-based early warning system that gathers preliminary reports of public health significance by monitoring global media sources in near 'real-time', 24 hours a day, 7 days a week basis. GPHIN is operated by the Public Health Agency of Canada, and monitors news sources and websites across the globe in 9 languages (e.g. English, French, Farsi, Portuguese, Arabic, Russian, Spanish, and Chinese simplified/traditional) (Keller, et al., 2009). While a series of algorithms are used and adjusted to capture relevant information, analysis of relevant data since 2003 was also carried out manually by a multidisciplinary and multilingual team of analysts. Permission for the study was granted by the School of Pharmacy Ethics Committee, Hatfield, UK (15 December, 2010; PHAEC/10-42).

3. RESULTS

Piracetam is sold online via illicit websites with no need for prescription (see Table 1). Some retailers require an initial ‘online consultation’ with an unknown ‘cyber-doctor’ before shipping their products in return for online credit-card payment. Products are then sent directly to the buyers, but these are often counterfeits as recently alerted by the US Food and Drug Administration (FDA) (2010).

Prices of piracetam vary according to the retailers from about 0.70 to 1.10 € for 1 gram; it is mainly sold in form of tablets and bulk powder (Nootropic reviews, 2013; Nootrabiolabs, 2013) (Table 1). Videos on the YouTube featuring how to use piracetam, where to get it, its effects and its dosages

also emerged from our searches (Piracetam Smart Drug Secret, 2010; Smart drugs make learning easier, 2010; Piracetam Review, 2011).

A summary of the characteristics of the non-medical use of piracetam is showed in Table 2.

3.1 Piracetam as a cognitive enhancer for non-medical purposes

Piracetam appears to be widely used by healthy individuals to enhance cognitive functions in study and work-related performances. The majority of the users report satisfactory improvements in different cognitive functions including learning, memory, concentration and ‘verbal intelligence’. It is taken orally with dosages up to 9.6 g/die. It is often assumed in concomitance with other psychoactive supplements including choline, caffeine, adderall and acetylcarnitine (Drugs-forum, 2006a; Longecity, 2007; Brainmeta, 2011). A selected number of personal accounts has been reported in Table 3.

3.2 Piracetam as a recreational drug

In addition to its cognitive enhancing features, piracetam is widely used from polydrug abusers for its psychedelic effects. It appears to have hallucinogenic and mood improving effects and appears to enhance dream experiences. It is taken orally at dosages up to 80 g/die or through nasal insufflations at dosages up to 7 g/die. Piracetam is often ingested in combination with other recreational drugs to enhance the power of their positive effects, to reduce their unwanted negative effects and to improve sensory feelings. In particular, there are several reports about its concomitant use with ketamine, methamphetamine, LSD, cocaine, alcohol, and kratom (Drugs-forum, 2005; Drugs-forum, 2006b; Drugs-forum, 2009a; Drugs-forum, 2009b; Drugs-forum, 2011; Erowid Experience Vault, 2007; Erowid Experience Vault, 2008). Some relevant users’ experiences are reported in Table 3.

3.3 Unwanted effects

Several misusers reported unwanted side effects related to Piracetam. The severity of the effects seems to be dose-dependent; however, as the online sources are largely imprecise, it is not possible to postulate a clear relation between dosages and effects. The unwanted side effects reported from Piracetam misusers include psychomotor agitation, dysphoria, 'feeling weird', tiredness, dizziness, memory loss, headache and severe diarrhoea; moreover, several users declared to not have felt any cognitive improvement nor psychedelic effects (Drugs-forum, 2005; Drugs-forum, 2006b; Drugs-forum, 2011).

4. DISCUSSION

To the best of our knowledge, this is the first study on the non-medical use of piracetam, which uncovers previously unknown psychoactive effects.

Prescription drugs such as piracetam are nowadays widely accessible on the web through online pharmacies (Schifano, et al., 2006). These are often illicit; they do not guarantee drugs' quality and, in 81.4% of cases, they sale medications without any medical prescription (Orizio, et al., 2009; Littlejohn, Baldacchino, Schifano, & Deluca, 2005). Marketing strategies are used to appear professional and trustable health websites, while showing pictures of doctors or licensed pharmaceutical products. In this context, it appears clear why the issue of the misuse of prescription drugs is continuously becoming more relevant (Bersani, et al., 2013; Schifano, et al., 2011; Schifano, et al., 2013).

In terms of misuse characteristics, piracetam can be considered both a 'common' recreational and a performance enhancing drug (Graham, et al., 2009) taken by individuals who aim to enhance their personal and professional performances. At the same time, as it emerged from online anecdotal reports examined in this study, they are usually aware that they do something unhealthy; for this reason, they are alerted about possible adverse effects that these products might induce and they are usually prepared to ask medical assistance, when necessary. On the other hand, they do not consider themselves drug addicts. This can lead to various health risks, including the consumption of

pharmaceutical product without any medical supervision, or a counterfeit medicine with unknown containing possibly toxic contaminants.

The misuse of piracetam to achieve enhanced professional results was found to be very popular; indeed, several reports were written in Italian (TGMOnline, 2008; Myhelpforum, 2012), and a range of related YouTube videos were here identified (Piracetam Smart Drug Secret, 2010; Smart drugs make learning easier, 2010; Piracetam Review, 2011). Most of the users feel safe with piracetam and it seems that the general belief is that piracetam can be taken at any dosage without any risk; this attitude probably stems from the high dosages of Piracetam usually prescribed by physicians (expressed in grams and not in milligrams) and from the general idea that something that is legal must necessary be safe (Corazza, et al., 2013). Conversely, the misuse of piracetam as a recreational drug seems to be limited to individuals, often marginalized, with a history of recreational polydrug misuse.

From a clinical point of view, although cases of piracetam dependence have not been described, physicians should be aware of Piracetam misuse issues, so that signs and symptoms of possible piracetam side effects may be recognized. Moreover, as Piracetam is often sold through unreliable online sources, misusers may present with an increased risk of ingesting a range of adulterated products with potential toxic effects (Evans-Brown, McVeigh, Perkins, & Bellis, 2012).

When considering the question of who might use online pharmacies to buy Piracetam or other drugs, it is possible to identify at least three prerequisites. These are (1) literacy: using the Internet to order drugs requires basic literacy and numeracy skills; (2) Internet access: the largest increase in Internet access has been seen in those with the highest incomes; and (3) credit-card ownership. In summary, these misusers are most likely to come from the socioeconomically privileged sections of society, where high levels of education and employment are likely to be the rule rather than the exception. For these reasons, the stereotypical image of the 'drug abusing patient' may need to change, in favour of a new class of 'expert' patients who use a website to obtain a self diagnosis and a treatment.

One could wonder about the limitations of carrying out a risk of misuse assessment of a drug whilst taking into account the online comments only; in fact, it may be inappropriate to trust information obtained from the Internet without independent verification. However, in absence of relevant peer-reviewed data, this seems to be the only method to obtain preliminary information about new and emerging phenomena (Schifano, et al., 2003; Schifano, et al., 2010); moreover, the web monitoring has proved that Internet is an important source of information for understanding users' point of view about the effects of drugs: writing in a web forum allows the user to hide his/her personal information and to write without any hesitation.

Declaration of Interest

The authors report no conflicts of interest.

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<p>http://www.northdrugstore.com/buy-Nootropil.html</p>	<p>Nootropil 800mg 90 pills \$29.00 Nootropil 800mg 180 pills \$49.00 Nootropil 800mg 270 pills \$69.00 Nootropil 800mg 360 pills \$85.00 Nootropil 1200mg 60 pills \$40.00 Nootropil 1200mg 120 pills \$75.00 Nootropil 1200mg 180 pills \$99.00 Nootropil 1200mg 240 pills \$125.00 Generic Piracetam 400mg 100 pills \$20.00 Generic Piracetam 400mg 200 pills \$35.00 Generic Piracetam 400mg 300 pills \$49.00 Generic Piracetam 400mg 400 pills \$65.00</p>
<p>http://www.nootrabiolabs.com/index.php?route=product/search&filter_name=piracetam</p>	<p>Piracetam 100g bulk powder \$ 9.99 Piracetam 200g bulk powder \$ 19.99 Piracetam 500g bulk powder \$ 47.99</p>

Table 1. Examples of Piracetam prices reported in pharmacies on line

Reasons	Descriptions
Online availability	Piracetam is easy to purchase over the Internet, where it is sold at a discounted rate and may be adulterated
Price	Prices of Piracetam sold online vary from about 0.70 to 1.10 € for 1 gram;
Effects	Improvement in learning, memory, concentration and “verbal intelligence”; hallucinations; mood improvement; enhancement of dream experiences
Dosages and way of assumption	As a cognitive enhancer it is taken orally with dosages up to 9.6 g/die. As a psychedelic drug it is taken orally at dosages up to 80 g/die or through nasal insufflations at dosages up to 7 g/die
Use in combination with other substances	It is often assumed in concomitance with other cognitive enhancers such as choline, caffeine, adderall and acetylcarnitine or other psychoactive drugs such as ketamine, methamphetamine, LSD, cocaine, alcohol, and ‘kratom’/Mytragina speciosa
Side effects	Psychomotor agitation, dysphoria, “feeling weird”, tiredness, dizziness, memory loss, headache and severe diarrhea
Misusers	Misusers are generally students who use piracetam to improve their cognitive performances and/or polydrug abusers who use it to experience a range of psychedelic states

Table 2: Summary of the characteristics of the non-medical use of Piracetam

Piracetam as a cognitive enhancer for non-medical purposes
<i>I am studying spanish right now pretty intensely, and piracetam is one of many among my supplement arsenal. I can tell you that it is much easier for me to memorize vocab and verbs. Also, I am becoming more and more fluent by the day. I believe that piracetam is enabling me comprehend and conversate in spanish very well. Granted, I took 3 years in high school and 3 quarters in college, but now that I am self-learning "the rest", it is all coming together quite nicely. Piracetam provides me with extreme focus and an unreal ability to memorize though (Longecity, 2007).</i>
<i>I take 1.2-1.6 g of piracetam 3 times a day 4-5 hours spaced out between dosages. I take around 1.5-2.1g of choline bitartrate with my breakfast. I would also add some acetyl-l-carnitine to the mix, around 1-3 g a day. The dosage, I believe, have a whole lot to do with the end-product you will experience. Superhuman memory? Well, just as a little marker of results, I've been periodically tested my digit span on the braingle site. I'm up to 14 now (Treato, 2013).</i>
<i>I've used 1000mg of piracetam with 500mg choline source. It works, whatever that means. You feel more articulate and you can literally feel your head throb. I found improved verbal intelligence more than anything. Everything seemed to require less effort, there were less mental blocks etc. I noticed my typing speed improved, although I made more spelling errors (Brainmeta, 2011).</i>
<i>SWIM often used caffeine (500-600mg) with an attack dose of piracetam (8000mg) for staying awake at night for learning. The combo works well, it really helps SWIM focus (Drugs-forum, 2006b).</i>
Effects of Piracetam as an hallucinogenic/recreational drug
<i>Back in the store, the colors and the entire scene stood out to me. In particular, I had a slightly empathic experience where I felt the negative/fear/frustration energies of all the people in the room (Erowid Experience Vault, 2007).</i>
<i>I noticed that the right side of my body is more closed up than the left side and it seemed that I was able to direct an inner energy-flow so that the right side could open up and I became more balanced (Erowid Experience Vault, 2008).</i>
<i>YES YES YES! It has been so relaxing! The music sounded more clear and detailed than usual and my attention was completely in it. I feel unusually fresh and fit, no more tiredness! Suddenly I started to dance spontaneously in my room (on music), just because it felt good, very satisfying! I was much more aware of /incontact-with my body (Erowid Experience Vault, 2008).</i>
<i>The most worthwhile use SWIM has found for this substance was for enhancing dreams. 1-2g taken before going to bed was found to enhance dream recall and vividness, helping SWIM wake more often with the feeling that the night had been at least as long and eventful than the day before in waking reality (Drugs-forum, 2008).</i>
Effects of Piracetam in combination with other recreational drugs
<i>Yet all of Piracetam + LSD trips had one thing in common - they were profoundly powerful, although LSD dosage was 1/4 to 1/2 of what I usually take without Piracetam (Erowid Experience Vault, 2001).</i>
<i>It increases many folds effects of stimulants and hallucinogens, while decreases or eliminates negative symptoms (Erowid Experience Vault, 2001).</i>
<i>SWIM has found it to inhibit the action of Ketamine, though SWIM wished it had done so more the last time he sat on the edge of a bed trying to persuade his hands to cram Piracetam pills in his mouth after a 250mg K nightmare. SWIM has really tried to like that substance but it seems like K and SWIM just aren't meant for each other (Drugs-forum, 2006b).</i>
<i>Meth is more intense, more happy, I need a lot less of meth, if combining it with 2400 mg of Piracetam. The most important part however is that even though I usually have a very hard crash from meth, accompanied by painful cravings, Piracetam seem to eliminate it totally. I just gradually come down and go to sleep (Erowid Experience Vault, 2001).</i>

Table 3. Relevant users' experiences in relation to Piracetam misuse. SWIM: Someone Who Is Not Me; Met: Methamphetamine; K: Ketamine