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Use of benzylglycinamide by a HIV-seropositive polysubstance user: the changing pattern of novel psychoactive substance use among youths

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Abstract

A 24-year old woman with multisubstance use since the age of 13, including opioids and cocaine, and long-standing HIV/HCV seropositivity status, presented with psychosis, agitation, and insomnia at the emergency department of a

university hospital. She had been abusive and physically aggressive frequently without specific reasons and was involved in criminal legal cases. She was hospitalized twice. During her first hospital stay she experienced a brief episode of detachment from her environment, similar to episodes reportedly suffered at home. Psychosis had developed following heavy polysubstance abuse. Her mother provided sachets containing benzylglycinamide, a substance with no known psychotropic effects, which were also present in the patient's urine. She was occasionally positive for cannabinoids. She used to buy various novel psychoactive substances (NPSs) from the internet and used experimentally various substances freely made available to her by drug suppliers/dealers. She was unable to explain clearly why she was taking any of the identified NPS. She stated she was taking benzylglycinamide to calm her when smoking synthetic cannabinoids. While it appears that benzylglycinamide is not likely to constitute a novel drug of abuse, her polysubstance use exemplifies trends in NPS use patterns among the youths in the Western world and should alert mental health workers as to the possible dangers of such behavior and its reflection on social behavior and psychopathology.

Key words: New Psychoactive Substances; Drug abuse; Benzylglycinamide; Drug-induced psychosis; HIV infection; HCV infection

1. Introduction.

Benzylglycinamide is virtually absent in the medical literature, save for two papers, one not relevant and another dealing with the antiepileptic properties of glycine amide derivatives, which found *N'*-benzylglycinamide to be inactive in mixed-breed dogs (Sussan, Dagan, Blotnik, & Bialer, 1999). Extending our PubMed strategy to ((glycineamide OR glycinamide OR "glycine amide" OR "benzyl glycinamide" OR benzylglycinamide) AND (addiction OR abuse OR mental OR brain)) NOT (prolyl-leucyl-glycinamide OR Pro-Leu-Gly OR PLG OR MIF-I OR melanocyte) yielded 72 papers as of August 25, 2015, six of which were of some relevance. Glycinamide has been found to facilitate NMDA receptor activity (Rao, Cler, Emmett, Mick, Iyengar, & Wood, 1990), to induce antinociception (Beyer, Komisaruk, González-Flores, & Gómora-Arrati, 2013) in rodents, and to oppose the effect of dizocilpine, a NMDA channel inhibitor, similarly to clozapine in rabbits (Hoffman & Basurto, 2014). Given that its effect on the NMDA receptor is opposite to that of the abused drugs ketamine and phencyclidine, it would be surprising that it could be abused. The cerebral effects of benzylglycinamide have still to be investigated.

We describe the case of a young woman with human immunodeficiency virus (HIV) and Hepatitis C virus (HCV) infections, who had multisubstance use and subsequently developed psychosis and who used N'-benzylglycinamide as a complementary recreational substance. The patient had purchased the substance through the internet and her biological fluids were positive for the drug. Asked why she used the drug, she could recall only poorly that it helped her to calm down. This case may exemplify the changing pattern of drug use in young people in the Western world.

2. Case presentation. A woman aged 24 was brought 31 months ago to the emergency department (ED) of our hospital with psychomotor agitation, dysphoria, accelerated and pressured speech, aggression, insomnia with impaired sleep-wake cycle, emotional instability, irritability, and rage bouts. She was not delusional. She was under juridical restriction at that time. At the ED screening (consisting of a urine immunofluorescence assay seeking paracetamol, amphetamine, methamphetamine, barbiturates, benzodiazepines, cocaine, methadone, opiates, phenylcyclidine, tetrahydrocannabinol, and tricyclic antidepressant drugs) she was positive for cannabinoids in her urine.

She was voluntarily admitted to our psychiatric facility, but left the ward four days. Her diagnosis was substance abuse, unspecified, and substance-related mood disorder. Since she was positive for human immunodeficiency virus (HIV), we confirmed her efavirenz/emtricitabine/tenofovir combination and started her on aripiprazole, 15 mg/day,

and promazine, 30 mg/day. She was referred back to the Community Drug Abuse service, where she was being followed-up.

Her clinical history was unremarkable; her 5-years-older sister had used drugs since the age of 12. Her parents had divorced when the patient was 8 years old; the two sisters went to live with their mother. Her father was emotionally detached and showed poor rapport with family members. She started occasional cannabis abuse at age 13, but one year later she was abusing it continuously. As a result she impaired important social relationships and suffered educational failure. She subsequently quit cannabis and started abusing alcohol, cocaine, and amphetamines. Her abuse was most intense during rave parties, which she strongly pursued. Once, at age 16, after having disappeared for two days, she was found living with a convicted drug smuggler in poor hygienic conditions. During this period she also abused intravenous heroin and was convicted of robbery. When she was 17 she was admitted to a dual diagnosis facility of a psychiatric hospital, where she stayed for three months. She was diagnosed as having substance use disorder (heroin) and hepatitis virus C infection (HCV). As soon as she reached adult age, she asked to be discharged against her doctors' advice and left the hospital at her own will. She quit school and after one year of substance abuse, sexual promiscuity, and law-breaking events, at age 19 she joined a substance detoxification community, where she stayed for one year and followed detoxification programs, with little benefit. She returned home and received a HIV diagnosis. As a consequence, she was treated at age 20 with efavirenz/emtricitabine/tenofovir. She had not given-up her multisubstance use, but rather extended it by smoking synthetic cannabinoid preparations.

On 15 May 2013 she returned to the ER, with severe insomnia, a clinical picture similar to the one of her first presentation, but during this second hospitalization she was also delusional and persecutory. She stayed for one week and was treated with 2 mg/day risperidone, gabapentin 900 mg/day, clonazepam, 4 mg/day, and the antiretroviral drug combination 25 mg rilpivirine, 200 mg FTC (emtricitabine), and 245 mg tenofovir. Her delusions had subsided by her discharge. In July 2013 she was twice hospitalized elsewhere after two distinct episodes of "speedball" overdose (intravenous heroin and cocaine), that had caused her loss of consciousness. In both cases she quit the hospital after a brief stay.

During August 2013, her mother reported she had been unresponsive in a couple of instances, fixing a remote point with her gaze and remaining mute. Episodes lasted 5-10 minutes each. She retained no memory of these episodes of

apparent absence. On September 12, 2013, she was referred with a request for compulsory psychiatric admission to the emergency room of our hospital. She was accompanied by her mother and showed reduced emotional expression, dysphoria, and restlessness; she was oppositional and loquacious, with accelerated speech. The patient was in a home confinement status after an arrest for an incongruent car robbery attempt. She eventually accepted hospitalization in our psychiatric ward. In the last few days before being proposed for compulsory hospitalization, she had been emotionally unstable, aggressive, persecutory, suspicious, and had bizarre thinking (she had pled for being forgiven by her mother because she had to change her sex after being imposed to do so by unspecified individuals).

During this hospitalization she denied using any drug and was negative on standard screening. Despite that, she had a five-minute episode of unresponsiveness while dining. Neurological examination and standard and sleep-deprived EEG showed no abnormality. Magnetic resonance imaging of the brain showed right frontal and parietal subcortical glial foci, which were non-specific and of unclear significance. We suspected that these “absence” episodes could be due to illicit drug use and informed her mother, who brought us sachets of white powder that her daughter was hiding in her room. We obtained blood and urine samples which we sent with the sachets to the Pavia Poison Control Centre, the clinical-toxicological coordinating Centre of the National Early Warning System (N.E.W.S), in collaboration with the Department of Anti-Drug Policies, Italian Government, Presidency of the Council of Ministers, Rome, Italy. However, the patient denied using any drug. The advanced 2nd-level targeted and non-targeted analysis consisted of liquid and gas chromatography/mass spectrometry (LC-MS and GC-MS) to search in urine for atropine, scopolamine, methoxetamine, ketamine and its metabolite norketamine, butylone, mephedrone, methylenedioxypyrovalerone (MDPV), dimethylcathinone, buphedrone, ethcathinone, 4-fluoro-methcathinone, pentedrone, methedrone, ethylone, pentylone, 1-Naphyrone, 4-methylethylketone (4-MEC), levamisole, 4-fluoro-amphetamine (4-FA), p-methoxetamine (PMA), methylenedioxyaminoindane (MDAI), p-methoxymethamphetamine (PMMA), aminopropyl benzofuran isomers (5/6 APB), dimethyltryptamine (DMT), 4-bromo-2,5-dimethoxyphenylethylamine (2-CB), 4-iodo-2,5dimethoxyphenylethylamine (2C-I), 2,5-dimethoxy-4-propylthiophenylethylamine (2C-T-7), and 2,5-dimethoxy-4-bromoamphetamine (DOB). Screening for synthetic cannabinoids in blood was performed with LC-MS and regards the following: JWH-007, JWH-016, JWH-018, JWH-019, JWH-073, JWH-081, JWH-098, JWH-122, JWH-147, JWH-200, JWH-250, JWH-302, JWH-398, RCS-4, RCS-8, AM-2201, MAM 2201, AM-2233, WIN-55212, WIN-48,098, and AM-694. The laboratory analysed the sachets and found benzylglycinamide.

She improved and was discharged after 20 days of hospitalization with 4 mg/day risperidone, lorazepam, 5 mg/day, and her previous antiretroviral drug treatment. She was transferred to a drug rehabilitation community by decision of the probate judge; she managed to escape after a two-month stay. Meanwhile, the Pavia Centre confirmed the presence of benzylglycinamide in patient's urine, while her blood sample was free from synthetic cannabinoids and other substances.

She eventually returned home in December 2013 where she discontinued all medications, resuming heavy cannabinoid, heroin, and alcohol use. She was well for one month, but in February 2014 she manifested incongruent behavior, with bizarre and sexual delusions (she masturbated compulsively to turn her menses back, while she believed she could become pregnant only if a penis could penetrate in her coccygeal cyst), and probable auditory hallucinations (speaking alone). Her mother would later tell us that during this period she frequently visited internet sites to seek NPSs. She accessed the ED twice due to agitation (3 and 28 of March, 2014), subsequently running away. Her urine was positive for cannabinoids, paracetamol, and opiate derivatives the first time and for cannabinoids only, the second time.

She became increasingly aggressive and was sentenced to further two months of imprisonment for robbery. Nevertheless, she continued staying at home, where she destroyed a wardrobe and was verbally and physically aggressive towards her mother. She was persuaded by her mother to re-establish contact with the local mental health department, but on 3 of April she assaulted a bystander, causing him a zygomatic bone fracture. The Police arrested her and brought her compulsorily to the ED; subsequently she was hospitalized in our psychiatric department. On her arrival she was mute, with psychomotor retardation, and progressively became oppositional, hostile, and eventually aggressive. We administered 5 mg risperidone, 2 mg desmethyldiazepam, 60 mg promazine, and reintroduced her previous anti-retroviral drug combination, despite her suspiciousness about it (she delusionally believed that the drug was made of eggshells that could harm her). At both ED and Pavia toxicological screenings she was clean for all drugs. When asked to respond why she took benzylglycinamide, for which she was found to be positive in urine on the previous occasion, she admitted having purchased the substance via the internet and that she was mixing it with tobacco to dull her senses. She could not recall exactly to which extent she obtained the desired effect. Her mother came with a bag full of glass vials and bottles with various powders which she said she found at home in a hidden place and which she reported that her daughter was mixing with normal tobacco and

marijuana. Bottles and vials were labeled with the chemical formula and production date (Figure 1). The patient told us she obtained them through the internet. We obtained her blood and urine samples and sent them together with the contents of the bottles to the Pavia Centre and to ADT, asking them to control whether the formulas and declared substances corresponded with the bottles' contents. ADT found bottles to contain different drugs, pro-drugs or by-products (Table 1) not corresponding to the labels.

She was discharged after a 21-day hospitalization with a diagnosis of ICD-9 "drug-induced delusional syndrome", roughly corresponding to DSM-5 substance-induced psychotic disorder, and with a prescription of 5 mg risperidone, 2 mg desmethyldiazepam, and the aforementioned anti-retroviral drug combination. Her probate judge ordered her to join a drug rehabilitative community in Turin, Northern Italy, where the patient awaited her trial. She remained there for about six months, until the end of her sentence. She returned home and suspended all drug treatment, included antiretroviral therapy. The patient went on to develop persecutory and bizarre delusions and became aggressive towards her mother in about two months. She was brought to the ED by the police and was subsequently compulsorily hospitalized in our department in January 7, 2015. Her toxicological analyses (blood and urine samples were collected and sent again to the Pavia Poison Control Centre) yielded no significant results. She stated she was no longer using any type of recreational drug. We prescribed paliperidone palmitate injections, 100 mg/30 days, 2.5 mg/day oral lorazepam, and 15 mg/day promazine in oral drops and reinstituted her antiretroviral regimen. During her hospital stay, her mother told us that her daughter was using experimental drugs that pushers were sending her freely to test the possible psychotropic effects of chemical synthesis drugs. This may explain why the patient could not give us an account of the bottles' content and also why she took drugs that produced no concrete psychotropic effect. At discharge she had improved, delusions were absent, but mood was dysphoric. Her CD4+/CD8+ ratio was within normal limits. She was sent back to the rehabilitative community, where she currently resides and is reportedly doing well. She and her mother signed free, informed consents for case publication.

3. Discussion

Novel psychoactive substance (NPS) use constitutes a new social behavioral pattern. It is facilitated by private chemical laboratory proliferation producing a host of novel substances to slip between legislative amendments and be sold legally until discovery of their abuse potential and subsequent regulation. People prone to experiment with NPS were termed "psychonauts" after Jünger's description of Arthur Heffter's behavior, a pharmacologist who had

described the effects of the newly discovered mescaline (Heffter, 1896) and peyote (Heffter, 1898) after having them tried himself. The spread of this recreational drug use pattern has as yet unknown social and individual effects, but for many connoisseurs of the issue, it bears a considerable threat potential (Schifano, 2001; Sacco & Finklea, 2014; Schifano, Orsolini, Papanti, & Corkery, 2015). Psychonauts are likely to engage in multiple substance use, without sticking to a particular drug. Our patient apparently abused drugs that are not likely to induce any particularly desirable effect that she knew from before. Her mother's suspicion was that her daughter was exploited by drug suppliers/dealers to probe the effects of unknown, experimental synthetic drugs. Her psychosis, mood instability, and uncontrollable impulsiveness, all secondary to compulsive substance abuse, combined with the threatening nature of HIV infection, rendered her vulnerable to exploitation. The patient used benzylglycinamide with no specific aim, just to test its possible effects. Her behavior, with her deliberate law infringement, her instability in accepting state-provided care, and her prompt abandonment of communities or hospitals, frame a background against which these new trends in drug use have to be viewed. The fact that she stored many vials containing substances with variable or questionable dependence/abuse-inducing potential may be taken to mean she was trying to modulate the effect of other drugs of abuse she was taking.

Among the drugs she possibly used (Table 1) concomitantly with synthetic cannabinoids and benzylglycinamide, none can be attributed the responsibility for her brief episodes of apparent detachment from environment. However, intake of no drug in Table 1 was consistent with the development of dissociative symptoms. Owing to their mechanisms, 4-piperidinone and 1H-indol-2-carboxylic acid could be related to anticonvulsant activity rather than seizures. Whether the detachment occurred due to the use or withdrawal of a given NPS is unclear, but the short half-time of benzylglycinamide (about 35 min in dogs and less than 1 hour in rats; Sussan et al., 1999) is unlikely to account for dependence or withdrawal. Dibenzylpiperazine, but not benzylglycinamide, could have been responsible for psychosis.

4. Conclusion

We described the use of benzylglycinamide in a patient with multisubstance abuse, HIV/HCV infection, and psychosis. The purpose of benzylglycinamide use cannot be probed, due to patient uncooperativeness. The possibility that similar patients may be at risk for being the experimental subjects of amoral drug suppliers/dealers

and other unlawful people should caution physicians to investigate these issues and raises heretofore unprecedented social issues.

Authors' disclosures

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Rao, T.S., Cler, J.A., Emmett, M.R., Mick, S.J., Iyengar, S., Wood, P.L. (1990). Glycine, glycinamide and D-serine act as positive modulators of signal transduction at the N-methyl-D-aspartate (NMDA) receptor in vivo: differential effects on mouse cerebellar cyclic guanosine monophosphate levels. *Neuropharmacology, 29*(11), 1075-1080.

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Figure caption

Figure 1. Bottles the patient purchased from internet sources, whose labels displayed chemical structures of substances claimed to be contained in them.

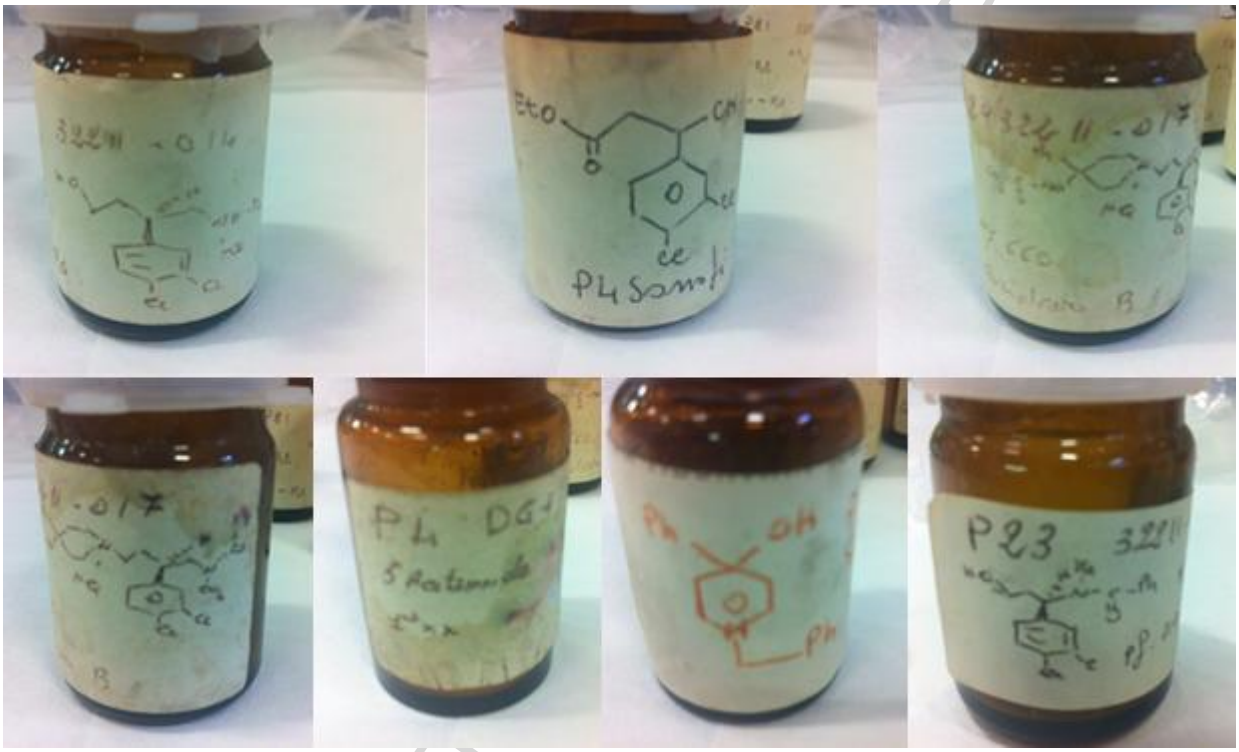
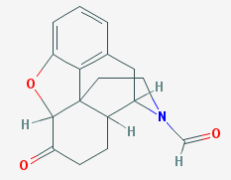
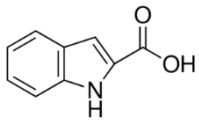
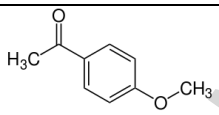
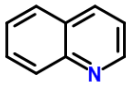
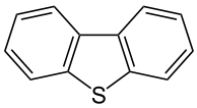
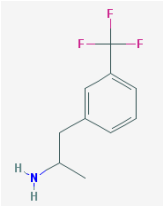
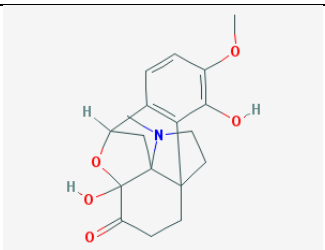
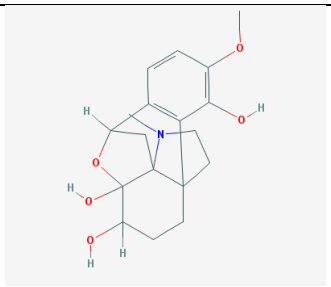
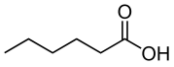
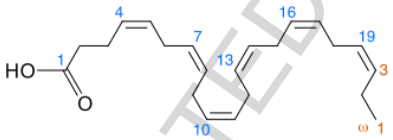
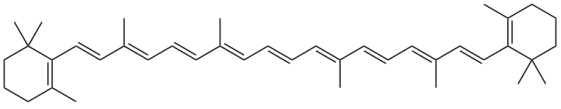
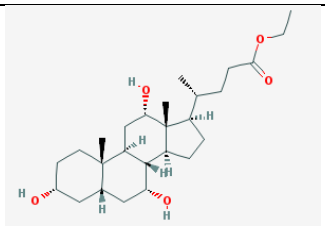
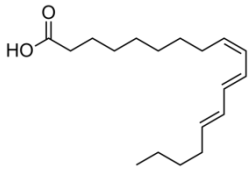
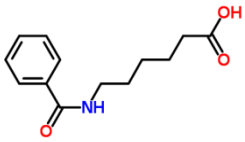
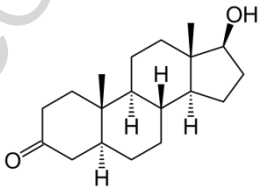
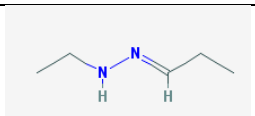
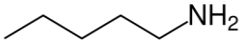
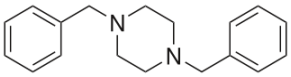
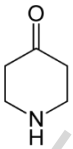


Table 1. Substances found in patient's bottles.

Substance	Chemical structure	Class/Mechanism	Commonly used in:
Dihydronor-morphinone		μ-opioid ligand	No known application; derivatives may possess analgesic properties
1H-Indol-2-carboxylic acid		Probably blocks NMDA glutamate receptors at their glycine sites	No known application; potential anti-obesity agent; putative anti-stroke, anti-head injury, anti-dementia and analgesic activity
1-(4-Methoxy-phenyl)ethanone		A terpene, may have activity on CB receptors	Cigarette cutting and flavoring in foodstuff
Quinoline		Prevents polymerization of toxic haem by forming a complex with haem, thus terminating chain extension	Cigarette additive, production of dyes, used in preparation of other chemicals; contained in anti-malarial agents
Dibenzothiophene		Heterocyclic derivative of polycyclic aromatic hydrocarbon, an agonist to the aryl hydrocarbon receptor	Used in cosmetics and pharmaceuticals; product of coal combustion
α-Methyl-*m*-trifluormethyl-Phenethylamine (Norfenfluramine)		Stimulant; calcium-independent 5-HT/NA releaser, potent 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} agonist	Appetite suppressant
Stephabyssine		*Stephania abyssinica* morphine and morphinandienone alcaloid, μ-opioid ligand	The plant is used as a folk remedy to treat asthma, tuberculosis, dysentery,

			hyperglycemia, malaria and other conditions
Stephaboline		*Stephania abyssinica* morphine and morphinandienone alcaloid, μ-opioid ligand	Same as above
Hexanoic acid (caproic acid)		Carboxylic acid; fibrinolysis inhibitor; facilitates passage of insulin through mucosal epithelia	Component of vanilla; used as flavoring agent in butter, milk, cream, strawberry, bread, beer, and nut flavors
Docosahexaenoic acid		Polyunsaturated ω_3 fatty acid; conjointly with uridine and choline, ↑ synthesis and levels of phosphatides and pre- and postsynaptic proteins, and ↑ formation of dendritic spines	Diets, cognitive decline, prodromal states
β-Carotene		Provitamin A, terpenoid hydrocarbon, nonpolar, fat soluble vitamin with antioxidant activity when beta-carotene 15,15'-monooxygenase converts it to retinol, which binds nuclear receptors and affects gene expression	Vitamin A deficiency may lead to keratomalacia, loss of night vision, xerophthalmia and other ocular conditions and supplements are used to contrast them; other medical uses include hepatic failure and porphyrias

Ethyl-iso-allocholate		A steroid from *Cenchrus ciliaris*; acts through nuclear steroid receptors	Biliary acid oil emulsifier
Octadecatrienoic acid		ω_3 Fatty acid; enhances choline acetyltransferase activity and ↑social interaction in post-weaning mice; antioxidant; antithrombotic activity?	Dietary
Benzoylamino-hexanoic acid		Carboxylic acid; derivatives inhibit mitotic centromere-associated kinesin (MCAK) ATPase activity; probable cytostatic activity (tumor growth and cell cycle progression and endoreduplication)	No particular use
Dihydrotestosterone		Androgenic steroid; acts through nuclear receptors to affect DNA expression; may cause male baldness and benign prostatic hyperplasia and increase aggression	Body building
N-acetyl-Valine		Amino acid	Product of acetylation of an L-amino acid used in the synthesis of pharmaceuticals
Ethylhydrazone		Aldehyde	Organic pollutant. No medical or industrial use
Pentanamine		Amine, possible stimulant	Flavoring agent used as

			a solvent and in the manufacture of dyes, emulsifiers, and pharmaceuticals
Dibenzylpiperazine		Piperazine derivative often found as an impurity in the recreational stimulant drug benzylpiperazine (BZP); when combined with MDMA may induce psychosis or death	Stimulant, recreational
4-Piperidinone		Piperidinone (piperidine derivative); curcumin analogue, may be cytostatic. 2-Piperidinone potentiates $GABA_A$-mediated currents and may be anticonvulsant	Intermediate in the manufacture of chemicals and pharmaceutical drugs (e.g., fentanyl)

Highlights

- Benzylglycinamide (BGA) has never been reported as a drug of abuse
- We report on a patient with psychosis with documented BGA abuse
- Patient claimed that the addition of BGA to cannabinoids helped her to calm