

DEBATE

Open Access

Amphetamine-induced psychosis - a separate diagnostic entity or primary psychosis triggered in the vulnerable?

Jørgen G Bramness^{1*}, Øystein Hoel Gundersen¹, Joar Guterstam², Eline Borger Rognli¹, Maija Konstenius², Else-Marie Løberg³, Sigrid Medhus¹, Lars Tanum¹ and Johan Franck²

Abstract

Use of amphetamine and methamphetamine is widespread in the general population and common among patients with psychiatric disorders. Amphetamines may induce symptoms of psychosis very similar to those of acute schizophrenia spectrum psychosis. This has been an argument for using amphetamine-induced psychosis as a model for primary psychotic disorders. To distinguish the two types of psychosis on the basis of acute symptoms is difficult. However, acute psychosis induced by amphetamines seems to have a faster recovery and appears to resolve more completely compared to schizophrenic psychosis. The increased vulnerability for acute amphetamine induced psychosis seen among those with schizophrenia, schizotypal personality and, to a certain degree other psychiatric disorders, is also shared by non-psychiatric individuals who previously have experienced amphetamine-induced psychosis. Schizophrenia spectrum disorder and amphetamine-induced psychosis are further linked together by the finding of several susceptibility genes common to both conditions. These genes probably lower the threshold for becoming psychotic and increase the risk for a poorer clinical course of the disease. The complex relationship between amphetamine use and psychosis has received much attention but is still not adequately explored. Our paper reviews the literature in this field and proposes a stress-vulnerability model for understanding the relationship between amphetamine use and psychosis.

Keywords: Drug induced psychosis, Amphetamine, Methamphetamine, Primary psychotic disorder, Schizophrenia

Background

Amphetamine and methamphetamine (hereafter amphetamines) can prolong wakefulness, increase focus and feelings of energy as well as decrease fatigue. They can produce euphoria, induce anorexia, and be used to treat narcolepsy and attention deficit/hyperactivity disorder (ADHD). Adverse effects include anxiety, aggression, paranoia, hyperactivity, reduced appetite, tachycardia, increased breathing rate, dilated pupils, increased blood pressure, headache, insomnia, palpitations, arrhythmia and others [1].

Amphetamines inhibit dopamine reuptake by interacting with the dopamine transporter (DAT), thereby increasing the concentration of dopamine in the synaptic

cleft [2]. Amphetamines also interact with the vesicular monoamine transporter 2 (VMAT2), leading to increasing amounts of dopamine in the cytosol, a possible mechanism of action for the neurotoxicity of amphetamines. Neurotoxic effects are seen also in serotonergic and noradrenergic neurons.

Amphetamines are highly addictive drugs. Both amphetamine and methamphetamine act directly on the mesolimbic dopaminergic “reward system” [3] by inducing release of dopamine, and to some extent norepinephrine, in the synaptic clefts of the Nucleus Accumbens (NAc) and other terminal areas provoking a euphoric state, but also addiction.

Abuse of amphetamines is widespread in the general population [4-9]. It is also common among psychiatric patients [10,11], where a high percentage test positive for amphetamines [12].

* Correspondence: j.g.bramness@medisin.uio.no

¹Norwegian Centre for Addiction Research (SERAF), Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Full list of author information is available at the end of the article

There is overwhelming evidence that patients with psychotic disorders have an increased vulnerability to compulsive use of drugs of abuse [13,14], including psycho stimulants like amphetamines [15]. This may be especially true for patients with schizophrenia like disorders [16]. There may be several explanations for this increased co morbidity, but there is convincing evidence from animal studies that this may be due to shared vulnerabilities for both psychosis and drug use disorders [17]. These animal studies also point to possible neural mechanisms explaining the increased co morbidity [18].

The association between amphetamine use and psychosis has received much attention [19], but several questions about this complex relationship remain unanswered. In the following, we review some of these questions and propose a new model for understanding the relationship between amphetamine use and psychosis.

Prevalence and clinical presentation

Observations strongly suggest a relationship between the intake of amphetamines and the development of acute psychosis. First, early studies demonstrated that amphetamines could trigger acute psychosis in healthy subjects. In these studies, amphetamine was given in consecutively higher doses until psychosis was precipitated, often after 100–300 mg of amphetamine [20-23]. The symptoms subsided within 6 days. The effect was blocked by the use of anti-psychotics [24]. Not all the subjects in these studies became psychotic, as some had to be removed from the experiment because of health risks caused by elevation of heart rate, blood pressure or body temperature. Secondly, psychosis has been viewed as an adverse event, although rare, in children with ADHD who have been treated with amphetamine [25-30]. Thirdly, drug-induced psychosis has been reported in 8–46% of regular users of amphetamines [31-37]. The wide variation is probably due to different populations being studied, gender [38] and the method and duration of amphetamine use [39]. It may also depend on the instruments used to assess psychosis, e.g. self-report [36] vs. formal diagnostic instruments [31,40]. Lastly, there is a positive correlation between amphetamine availability at a community level and the incidence of psychosis in the same population [41-44].

Amphetamine has a terminal elimination half life ($T_{1/2}$) of 12–15 hours [45] and is often taken several times over the course of many days in runs or binges [46-49]. There is clinical evidence that such binges may end in psychosis. Surprisingly, it is poorly understood [1,50], whether such psychosis is due to amphetamine use *per se* (amount over time, amount on one occasion or the length of the current binge), vulnerabilities in the user or both. It could be that psychosis occurs because of the sleep deprivation that follows amphetamine use, or

because of other factors at the end of a binge. Users will often end their binge by using sedating drugs like alcohol, benzodiazepines, opiates or cannabis. This could be viewed as self-medication [51] and may be one reason why users often develop problems with several drugs. Only a weak relationship has been reported between psychotic symptoms and the level of amphetamines in the blood of psychotic patients [51,52]. This could be because acute blood levels at the end of a binge are a poor representation of overall amphetamine exposure, but it could also be because individual vulnerability, rather than level of amphetamine exposure, is the critical risk factor for developing acute psychosis.

The symptoms of psychosis induced by amphetamines are very similar to those of acute schizophrenia spectrum psychosis and include: lack of concentration, delusions of persecution, increased motor activity, disorganization of thoughts, lack of insight, anxiety, suspicion and auditory hallucinations [21,22,53]. Some studies have suggested differences with more pronounced grandiosity and visual hallucinations [52,54]. The thought disorders that occur in schizophrenia characterized by a splitting and loosening of associations, a concreteness of abstract thought, and an impairment in goal-directed thought, may be less prominent in amphetamine induced psychosis [55]. However, distinguishing the two types of psychosis on the basis of acute symptoms is probably very difficult [56]. The similarities between the two conditions are, in fact, so pronounced that this has been used as an argument for using amphetamine-induced psychosis as a model for primary psychotic disorders [21,54,57-59].

In contrast to schizophrenic psychosis, acute psychosis induced by amphetamines seems to have a faster recovery [60-63], and appears to resolve with abstinence, although the recovery may be incomplete [43]. Japanese researchers have argued that psychosis induced by amphetamines could, in fact, be of much longer duration, up to several years [64-66]. This research describes spontaneous psychotic relapses in the long term after remittance of psychosis (“flashbacks”), a phenomenon acknowledged in the popular folk culture in the USA and Europe, but much less researched. Stressful situations seem to trigger such flashbacks in susceptible individuals and several vulnerability factors have been identified, e.g. a family history of psychosis [67-70]. It is difficult to distinguish the Japanese chronic amphetamine psychosis from a primary psychosis triggered by the use of amphetamines [64], although it has been claimed that they constitute separate entities.

Risk factors and acute vs. chronic psychosis

In animal models, there is sensitization to the rewarding effects of amphetamines (e.g. [71]). Sensitization is also seen in human subjects [72]. There is reason to believe

that an earlier psychosis involves a risk of future psychotic episodes due to this sensitization [43,73-75], or possibly to the development of dopaminergic super sensitivity [76,77]. Psychosis may be precipitated acutely by amphetamine due to its effects on dopaminergic activity in the CNS [46]. In the longer term, the neurotoxic effects of the drugs on serotonin and dopamine neurons [78] and dopamine transporters [79] may play a role. Amphetamine sensitization seems to cause dysregulation of dopamine by the ventral subiculum [80]. There is an over-expression of the dopamine receptor, subtype 2 (DRD2) [81] and a higher sensitivity of DRD2 to the effects of amphetamines in vulnerable individuals [82].

In addition to the increased risk of psychosis following the use of amphetamines in people who have experienced amphetamine-induced psychosis previously, patients with schizophrenia [83] and schizotypal personality traits [74,84] may more readily become psychotic after the use of amphetamines. Other risk factors for psychosis may include amphetamine use disorders (abuse and dependence), the presence of other psychiatric disorders (primarily attenuated psychosis syndrome, personality disorders and affective disorders), early cognitive dysfunction (such as those found in the prodromal states of schizophrenia), family history of mental disorder and the use of other drugs like opiates, benzodiazepines, cannabis and alcohol [37,67,74,75,85-87].

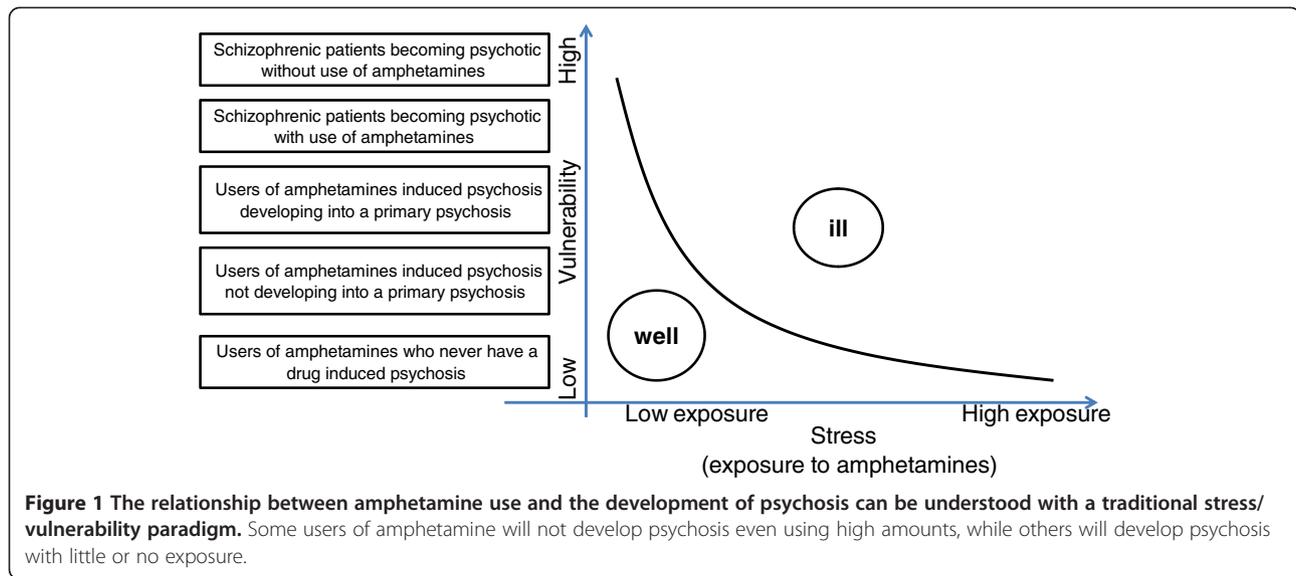
Several susceptibility genes have been found in common for amphetamine-induced psychosis and schizophrenia [32,58]. These genes increase the risk both for becoming psychotic and for a poorer clinical course of the disease. Studies in Japan also indicate that primary and drug induced psychosis may be genetically linked. Relatives of methamphetamine-users with a lifetime history of amphetamine psychosis are 5 times more likely to have schizophrenia than methamphetamine-users without a history of psychosis [85]. Patients with schizophrenia and those with psychosis induced by amphetamines both show significantly increased peripheral plasma levels of norepinephrine compared to methamphetamine users who do not have psychosis, and to non-using controls [65,88]. This seemingly common vulnerability is important considering the difficulties in distinguishing between the two conditions in the long term.

The precipitation of psychosis by amphetamines in healthy subjects can be blocked by anti-psychotics [24,89]. Similarly, psychotic symptoms caused by amphetamines can, like acute schizophrenic psychosis, be treated with anti-psychotics [90]. A Cochrane review from 2009 [91] identified only one randomized controlled trial of treatment for psychosis induced by amphetamines which met the criteria for included studies. It showed that both olanzapine and haloperidol in clinically relevant doses were effective in treating psychotic symptoms

[92]. One problem with using anti-psychotics could be that such drugs have a tendency to block the DRD2, potentially increasing anhedonia that could, in turn, cause a greater vulnerability to relapse into drug abuse. Some studies indeed point in this direction [93-95]. The use of alternative therapeutic drugs, such as benzodiazepines, will reduce the chance of extra pyramidal adverse effects [96] and decrease the risk of intoxication [97]. However, one argument against this strategy is that anti-psychotics seem to protect against the neurotoxic effects of amphetamines [98,99].

To further complicate the situation, it seems that up to 25% of those initially diagnosed with drug induced psychosis after some years develop a primary psychotic disorder [100], and even higher figures when looking at methamphetamine induced psychosis [67]. This leaves us with a dilemma - how valid is a diagnostic construct of amphetamine induced psychosis? Such a term suggests the assumption that this type of psychosis can be induced in individuals otherwise not susceptible to, e.g. schizophrenia or other primary psychotic disorders. The ambiguity and difficulties of this diagnosis are reflected in a recent review where the authors suggest the alternative term "substance-associated psychosis" and state that there is a dearth of research that rigorously examines the validity of the diagnostic criteria across substances [101]. These researchers identified 18 papers that specifically focused on delineating the clinical characteristics or outcomes of individuals diagnosed with substance-induced psychosis. Seven of these papers focused on stimulants (amphetamines and cocaine), but only one had a 1 year follow-up assessment.

Also for other substances of abuse with a tendency to cause psychosis there have been similar discussions. It has long been recognized that the use of cannabis in early adolescence increases the risk of later development of psychosis and schizophrenia [102,103]. Because the drug intake takes place many years before the diagnosis of schizophrenia it has been argued that this cannot be a case of reversed causality [104]. There are however some arguments in the opposite direction. Firstly, even with a formidable increase in the use of cannabis in the population, no increase in the incidence of schizophrenia has been observed [105]. Secondly, it has been shown that patients with schizophrenia may have their psychosis triggered by lower intake of cannabis than healthy volunteers [106]. Lastly, we do not know *when* a psychotic disorder starts to develop. It may be that it starts long before the initial psychotic symptoms, opening for the possibility of reversed causality, even when intake of cannabis takes place years before first psychotic episode [104]. The present agreement in the field seems to be that cannabis can precipitate psychosis in vulnerable individuals, an agreement that closely resembles our



suggested model. The similarities between amphetamines' and cannabis' risk of being associated with later psychosis is further supported by a newly published record linkage study [107].

A model for the relationship between psychosis induced by amphetamines and primary psychotic disorder

The similarities between acute schizophrenic psychosis and psychosis following the use of amphetamines are so pronounced that the latter has been suggested as a model for schizophrenia [58,108]. However, it remains unresolved whether the relationship between amphetamines and psychosis is explained by drug exposure (amphetamine-induced psychosis), amphetamines use triggering a primary psychotic disorder or both. Although psychosis may be induced by amphetamine in healthy individuals, not all subjects become psychotic by the doses of amphetamines allowed in the experiments. Some, but not all, individuals using amphetamines have experienced psychotic episodes, and a few have experienced psychosis as an adverse event during stimulant treatment. Is this a result of differences in amphetamine exposure or differences in vulnerability? Furthermore, psychosis is precipitated by a lower dose of amphetamines in individuals with primary psychosis and may be blocked by the use of anti-psychotics. Finally, there seem to be many genetic and physiological similarities between amphetamine-induced psychosis and acute schizophrenic psychosis, suggesting that vulnerability may play a significant role in the occurrence of amphetamines-induced psychosis.

In this context, we hypothesize that the relationship between amphetamine-induced psychosis and primary psychosis can be viewed within the framework of a traditional vulnerability stress paradigm (Figure 1). Exposure

to amphetamines should be viewed as a stressor in the acute phase for the vulnerable individual in a dynamic way; for individuals with lower vulnerability higher doses of amphetamines are needed, whereas individuals with higher vulnerability require lower doses to precipitate acute psychosis. In addition, due to their sensitizing effects, amphetamines may also play a role in the development of vulnerability. Repeated use of amphetamines could increase vulnerability, thereby increasing the chances of developing psychotic symptoms even in the absence of (acute exposure to) amphetamines. Thus, primary psychotic disorder and psychosis precipitated by amphetamines need not be considered as two separate phenomena, but as two phenomena interlinked in a dynamic way.

Taking such a view may have some important clinical implications. Patients diagnosed with drug induced psychosis following intake of amphetamines should be monitored more closely, in particular for signs of a chronic development. Any further use of amphetamines should be strongly discouraged, since it would constitute an acute stressor that could precipitate psychosis and increase the individual's vulnerability to developing a more chronic psychotic disorder. This model also provides a rationale for future studies of preventive anti-psychotic treatment, including psycho-social, psycho-educational and possibly also pharmacological interventions to decrease vulnerability, in the same way as is recommended for individuals with a primary psychotic disorder.

Competing interests

None of the authors have any conflicts of interest to declare.

Authors' contributions

All the authors have contributed substantially to the idea, structure and content of the paper. All authors have discussed all concepts and formulations in the final manuscript and have approved the submitted

versions. JGB has, as first author, written the first draft of all the sections, but these have been altered and reformulated by all the authors in several collaborating rounds.

Author details

¹Norwegian Centre for Addiction Research (SERAF), Institute of Clinical Medicine, University of Oslo, Oslo, Norway. ²Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden. ³Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway.

Received: 29 February 2012 Accepted: 11 September 2012

Published: 5 December 2012

References

- Lineberry TW, Bostwick JM: **Methamphetamine abuse: a perfect storm of complications.** *Mayo Clin Proc* 2006, **81**(1):77–84.
- Seiden LS, Sabol KE, Ricaurte GA: **Amphetamine: effects on catecholamine systems and behavior.** *Annu Rev Pharmacol Toxicol* 1993, **33**:639–677.
- Robinson TE, Berridge KC: **The psychology and neurobiology of addiction: an incentive-sensitization view.** *Addiction* 2000, **95**(Suppl 2):S91–S117.
- Degenhardt L, Roxburgh A, McKetin R: **Hospital separations for cannabis- and methamphetamine-related psychotic episodes in Australia.** *Med J Aust* 2007, **186**(7):342–345.
- Degenhardt L, Roxburgh A, Black E, Bruno R, Campbell G, Kinner S, et al: **The epidemiology of methamphetamine use and harm in Australia.** *Drug Alcohol Rev* 2008, **27**(3):243–252.
- Durell TM, Kroutil LA, Crits-Christoph P, Barchha N, Van Brunt DL: **Prevalence of nonmedical methamphetamine use in the United States.** *Subst Abuse Treat Prev Policy* 2008, **3**:19.
- Maxwell JC, Rutkowski BA: **The prevalence of methamphetamine and amphetamine abuse in North America: a review of the indicators, 1992–2007.** *Drug Alcohol Rev* 2008, **27**(3):229–235.
- McKetin R, Kozel N, Douglas J, Ali R, Vicknasingam B, Lund J, et al: **The rise of methamphetamine in Southeast and East Asia.** *Drug Alcohol Rev* 2008, **27**(3):220–228.
- Odegård Lund M, Skretting A, Lund K: **Rusmiddelbruk blant unge voksne, 21–30 år.** Oslo: Statens Institutt for Rusmiddelforskning; 2007.
- Gonzales R, Ang A, McCann MJ, Rawson RA: **An emerging problem: methamphetamine abuse among treatment seeking youth.** *Subst Abuse* 2008, **29**(2):71–80.
- Katz G, Durst R, Shufman E, Bar-Hamburger R, Grunhaus L: **Substance abuse in hospitalized psychiatric patients.** *Isr Med Assoc J* 2008, **10**(10):672–675.
- Mordal J, Bramness JG, Holm B, Morland J: **Drugs of abuse among acute psychiatric and medical admissions: laboratory based identification of prevalence and drug influence.** *Gen Hosp Psychiatry* 2008, **30**(1):55–60.
- Cantor-Graae E, Nordström LG, McNeil TF: **Substance abuse in schizophrenia: a review of the literature and a study of correlates in Sweden.** *Schizophr Res* 2001, **48**(1):69–82.
- Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, et al: **Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study.** *JAMA* 1990, **264**(19):2511–2518.
- Ringen PA, Melle I, Birkenaes AB, Engh JA, Faerden A, Vaskinn A, et al: **The level of illicit drug use is related to symptoms and premorbid functioning in severe mental illness.** *Acta Psychiatr Scand* 2008, **118**(4):297–304.
- Ringen PA, Lagerberg TV, Birkenaes AB, Engh J, Faerden A, Jonsdottir H, et al: **Differences in prevalence and patterns of substance use in schizophrenia and bipolar disorder.** *Psychol Med* 2008, **38**(9):1241–1249.
- Chambers RA, Krystal JH, Self DW: **A neurobiological basis for substance abuse comorbidity in schizophrenia.** *Biol Psychiatry* 2001, **50**(2):71–83.
- Chambers RA, Sentir AM, Engleman EA: **Ventral and dorsal striatal dopamine efflux and behavior in rats with simple vs. co-morbid histories of cocaine sensitization and neonatal ventral hippocampal lesions.** *Psychopharmacology (Berl)* 2010, **212**(1):73–83.
- Paparelli A, Di FM, Morrison PD, Murray RM: **Drug-induced psychosis: how to avoid star gazing in schizophrenia research by looking at more obvious sources of light.** *Front Behav Neurosci* 2011, **5**:1.
- Angrist BM, Gershon S: **The phenomenology of experimentally induced amphetamine psychosis—preliminary observations.** *Biol Psychiatry* 1970, **2**(2):95–107.
- Bell DS: **The experimental reproduction of amphetamine psychosis.** *Arch Gen Psychiatry* 1973, **29**(1):35–40.
- Griffith JJ, Oates J, Cavanaugh J: **Paranoid episodes induced by drugs.** *JAMA* 1968, **205**:36.
- Janowsky DS, Risch C: **Amphetamine psychosis and psychotic symptoms.** *Psychopharmacology (Berl)* 1979, **65**(1):73–77.
- Espelin DE, Done AK: **Chlorpromazine vs. amphetamine.** *N Engl J Med* 1968, **279**(6):329.
- Calello DP, Osterhoudt KC: **Acute psychosis associated with therapeutic use of dextroamphetamine.** *Pediatrics* 2004, **113**(5):1466.
- Lucas AR, Weiss M: **Methylphenidate hallucinosis.** *JAMA* 1971, **217**(8):1079–1081.
- Ross RG: **Psychotic and manic-like symptoms during stimulant treatment of attention deficit hyperactivity disorder.** *Am J Psychiatry* 2006, **163**(7):1149–1152.
- Spear J, Alderton D: **Psychosis associated with prescribed dexamphetamine use.** *Aust N Z J Psychiatry* 2003, **37**(3):383.
- Surles LK, May HJ, Garry JP: **Adderall-induced psychosis in an adolescent.** *J Am Board Fam Pract* 2002, **15**(6):498–500.
- Young D, Serorille WB: **Paranoid psychosis in narcolepsy and possible dangers of benzedrine treatment.** *Med Clin North Am* 1938, **22**(637):643.
- Glasner-Edwards S, Mooney LJ, Marinelli-Casey P, Hillhouse M, Ang A, Rawson R: **Clinical course and outcomes of methamphetamine-dependent adults with psychosis.** *J Subst Abuse Treat* 2008, **35**(4):445–450.
- Grant KM, Levan TD, Wells SM, Li M, Stoltenberg SF, Gendelman HE, et al: **Methamphetamine-Associated Psychosis.** *J Neuroimmune Pharmacol* 2011, **7**(1):113–139.
- Leamon MH, Flower K, Salo RE, Nordahl TE, Kranzler HR, Galloway GP: **Methamphetamine and paranoia: the methamphetamine experience questionnaire.** *Am J Addict* 2010, **19**(2):155–168.
- McKetin R, McLaren J, Lubman DI, Hides L: **The prevalence of psychotic symptoms among methamphetamine users.** *Addiction* 2006, **101**(10):1473–1478.
- Shoptaw S, Peck J, Reback CJ, Rotheram-Fuller E: **Psychiatric and substance dependence comorbidities, sexually transmitted diseases, and risk behaviors among methamphetamine-dependent gay and bisexual men seeking outpatient drug abuse treatment.** *J Psychoactive Drugs* 2003, **35**(Suppl 1):161–168.
- Wallace C, Galloway T, McKetin R, Kelly E, Leary J: **Methamphetamine use, dependence and treatment access in rural and regional North Coast of New South Wales, Australia.** *Drug Alcohol Rev* 2009, **28**(6):592–599.
- Yen CF, Chong MY: **Comorbid psychiatric disorders, sex, and methamphetamine use in adolescents: a case-control study.** *Compr Psychiatry* 2006, **47**(3):215–220.
- Mahoney JJ, Hawkins RY, De La Garza R, Kalechstein AD, Newton TF: **Relationship between gender and psychotic symptoms in cocaine-dependent and methamphetamine-dependent participants.** *Gen Med* 2010, **7**(5):414–421.
- Matsumoto T, Kamijo A, Miyakawa T, Endo K, Yabana T, Kishimoto H, et al: **Methamphetamine in Japan: the consequences of methamphetamine abuse as a function of route of administration.** *Addiction* 2002, **97**(7):809–817.
- Grant KM, Kelley SS, Agrawal S, Meza JL, Meyer JR, Romberger DJ: **Methamphetamine use in rural Midwesterners.** *Am J Addict* 2007, **16**(2):79–84.
- Medhus S, Mordal J, Holm B, Morland J, Bramness JG: **A comparison of symptoms and drug use between patients with methamphetamine associated psychoses and patients diagnosed with schizophrenia in two acute psychiatric wards.** *Psychiatry research* 2012.
- Sara G, Burgess P, Malhi G, Whiteford H: **Amphetamine availability and admissions for psychosis in New South Wales, 2001–2009.** *Aust N Z J Psychiatry* 2011, **45**(4):317–324.
- Ujike H, Sato M: **Clinical features of sensitization to methamphetamine observed in patients with methamphetamine dependence and psychosis.** *Ann N Y Acad Sci* 2004, **1025**:279–287.
- Vos PJ, Cloete KJ, Le RA, Kidd M, Jordaan GP: **A retrospective review of trends and clinical characteristics of methamphetamine-related acute psychiatric admissions in a South African context.** *Afr J Psychiatry (Johannesbg)* 2010, **13**(5):390–394.
- de la Torre R, Farre M, Navarro M, Pacifici R, Zuccaro P, Pichini S: **Clinical pharmacokinetics of amphetamine and related substances: monitoring in**

- conventional and non-conventional matrices. *Clin Pharmacokinet* 2004, **43**(3):157-185.
46. Segal DS, Kuczenski R: An escalating dose "binge" model of amphetamine psychosis: behavioral and neurochemical characteristics. *J Neurosci* 1997, **17**(7):2551-2566.
 47. Semple SJ, Zians J, Grant I, Patterson TL: Impulsivity and methamphetamine use. *J Subst Abuse Treat* 2005, **29**(2):85-93.
 48. Semple SJ, Zians J, Strathdee SA, Patterson TL: Psychosocial and behavioral correlates of depressed mood among female methamphetamine users. *J Psychoactive Drugs* 2007, **4**(Suppl):353-366.
 49. Williamson S, Gossop M, Powis B, Griffiths P, Fountain J, Strang J: Adverse effects of stimulant drugs in a community sample of drug users. *Drug Alcohol Depend* 1997, **44**(2-3):87-94.
 50. Volkow Nora D, NIDA Research Report: **Methamphetamine Abuse and Addiction**. Washington: National Institute on Drug Abuse; 2006.
 51. Medhus S, Mordal J, Holm B, Mørland J, Bramness JG: Symptoms and drug use among (meth)amphetamine positive patients admitted to the acute psychiatric ward. *Psychiatr Res* 2012, in press.
 52. Harris D, Batki SL: Stimulant psychosis: symptom profile and acute clinical course. *Am J Addict* 2000, **9**(1):28-37.
 53. Jonsson LE, Sjostrom K: A rating scale for evaluation of the clinical course and symptomatology in amphetamine psychosis. *Br J Psychiatry* 1970, **117**(541):661-665.
 54. Srisurapanont M, Ali R, Marsden J, Sunga A, Wada K, Monteiro M: Psychotic symptoms in methamphetamine psychotic in-patients. *Int J Neuropsychopharmacol* 2003, **6**(4):347-352.
 55. Yui K, Ikemoto S, Ishiguro T, Goto K: Studies of amphetamine or methamphetamine psychosis in Japan: relation of methamphetamine psychosis to schizophrenia. *Ann N Y Acad Sci* 2000, **914**:1-12.
 56. Srisurapanont M, Arunpongpaial S, Wada K, Marsden J, Ali R, Kongsakon R: Comparisons of methamphetamine psychotic and schizophrenic symptoms: a differential item functioning analysis. *Prog Neuropsychopharmacol Biol Psychiatry* 2011, **35**(4):959-964.
 57. Bell DS: Comparison of amphetamine psychosis and schizophrenia. *Br J Psychiatry* 1965, **111**:701-707.
 58. Bousman CA, Glatt SJ, Everall IP, Tsuang MT: Methamphetamine-Associated Psychosis: A model for Biomarker Discovery in Schizophrenia. In *Handbook of Schizophrenia Spectrum Disorders Volume 1*. Edited by Ritsner MS. Dordrecht: Springer Science+Business Media B.V; 2011:327-343.
 59. Ellinwood EH: Amphetamine Psychosis: I. Description of the Individuals and Process. *J Nerv Ment Dis* 1967, **144**(4):273-283.
 60. Connell PH: Amphetamine Psychosis. Maudsley Monograph No. 5. London: Oxford University Press; 1958.
 61. McIver C, McGregor C, Baigent M, Spain D, Newcombe D, Ali R: Guidelines for the medical management of patients with methamphetamine-induced psychosis. South Australia: Drug and Alcohol Services; 2006.
 62. Slater E: Book Review of "Amphetamine Psychosis" by P. H. Connell. *Br Med J* 1959, **21**:488.
 63. Yeh HS, Lee YC, Sun HJ, Wan SR: Six months follow-up of patients with methamphetamine psychosis. *Zhonghua Yi Xue Za Zhi (Taipei)* 2001, **64**(7):388-394.
 64. Grelotti DJ, Kanayama G, Pope HG Jr: Remission of persistent methamphetamine-induced psychosis after electroconvulsive therapy: presentation of a case and review of the literature. *Am J Psychiatry* 2010, **167**(1):17-23.
 65. Yui K, Ishiguro T, Goto K, Ikemoto S: Susceptibility to subsequent episodes in spontaneous recurrence of methamphetamine psychosis. *Ann N Y Acad Sci* 2000, **914**:292-302.
 66. Akiyama K: Longitudinal clinical course following pharmacological treatment of methamphetamine psychosis which persists after long-term abstinence. *Ann N Y Acad Sci* 2006, **1074**:125-134.
 67. Kittirattanapaiboon P, Mahatnirunkul S, Booncharoen H, Thummawong P, Dumrongchai U, Chutha W: Long-term outcomes in methamphetamine psychosis patients after first hospitalisation. *Drug Alcohol Rev* 2010, **29**(4):456-461.
 68. Yui K, Ikemoto S, Goto K: Factors for susceptibility to episode recurrence in spontaneous recurrence of methamphetamine psychosis. *Ann N Y Acad Sci* 2002, **965**:292-304.
 69. Yui K, Ikemoto S, Goto K, Nishijima K, Kato S: Susceptibility to episode recurrence in spontaneous recurrence of methamphetamine psychosis. *J Clin Psychopharmacol* 2003, **23**(5):525-528.
 70. Yui K, Goto K, Ikemoto S: The role of noradrenergic and dopaminergic hyperactivity in the development of spontaneous recurrence of methamphetamine psychosis and susceptibility to episode recurrence. *Ann N Y Acad Sci* 2004, **1025**:296-306.
 71. Robinson TE, Becker JB: Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. *Brain Res* 1986, **396**(2):157-198.
 72. Strakowski SM, Sax KW, Rosenberg HL, DelBello MP, Adler CM: Human response to repeated low-dose d-amphetamine: evidence for behavioral enhancement and tolerance. *Neuropsychopharmacology* 2001, **25**(4):548-554.
 73. Bartlett E, Hallin A, Chapman B, Angrist B: Selective sensitization to the psychosis-inducing effects of cocaine: a possible marker for addiction relapse vulnerability? *Neuropsychopharmacology* 1997, **16**(1):77-82.
 74. Chen CK, Lin SK, Sham PC, Ball D, Loh EW, Hsiao CC, et al: Pre-morbid characteristics and co-morbidity of methamphetamine users with and without psychosis. *Psychol Med* 2003, **33**(8):1407-1414.
 75. Vincent N, Schoobridge J, Ask A, Allsop S, Ali R: Physical and mental health problems in amphetamine users from metropolitan Adelaide, Australia. *Drug Alcohol Rev* 1998, **17**(2):187-195.
 76. Sato M: Long-lasting hypersensitivity to methamphetamine following amygdaloid kindling in cats: the relationship between limbic epilepsy and the psychotic state. *Biol Psychiatry* 1983, **18**(5):525-536.
 77. Sato M, Chen CC, Akiyama K, Otsuki S: Acute exacerbation of paranoid psychotic state after long-term abstinence in patients with previous methamphetamine psychosis. *Biol Psychiatry* 1983, **18**(4):429-440.
 78. Myers CS, Halladay AK, Widmer DA, Wagner GC: Neurotoxic effects of amphetamine plus L-DOPA. *Prog Neuropsychopharmacol Biol Psychiatry* 1999, **23**(4):731-740.
 79. Iyo M, Sekine Y, Mori N: Neuromechanism of developing methamphetamine psychosis: a neuroimaging study. *Ann N Y Acad Sci* 2004, **1025**:288-295.
 80. Grace AA: Dopamine system dysregulation by the ventral subiculum as the common pathophysiological basis for schizophrenia psychosis, psychostimulant abuse, and stress. *Neurotox Res* 2010, **18**(3-4):367-376.
 81. Abi-Dargham A, Rodenhiser J, Printz D, Zea-Ponce Y, Gil R, Kegeles LS, et al: Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *Proc Natl Acad Sci U S A* 2000, **97**(14):8104-8109.
 82. Seeman P: All Roads to Schizophrenia Lead to Dopamine Supersensitivity and Elevated Dopamine D2 Receptors. *CNS Neurosci Ther* 2010, **17**(2):1755-1759.
 83. Lieberman JA, Kane JM, Alvir J: Provocative tests with psychostimulant drugs in schizophrenia. *Psychopharmacology (Berl)* 1987, **91**(4):415-433.
 84. Tsuang MT, Simpson JC, Kronfol Z: Subtypes of drug abuse with psychosis. Demographic characteristics, clinical features, and family history. *Arch Gen Psychiatry* 1982, **39**(2):141-147.
 85. Chen CK, Lin SK, Sham PC, Ball D, Loh E, Murray RM: Morbid risk for psychiatric disorder among the relatives of methamphetamine users with and without psychosis. *Am J Med Genet B Neuropsychiatr Genet* 2005, **136B**(1):87-91.
 86. McKetin R, Hickey K, Devlin K, Lawrence K: The risk of psychotic symptoms associated with recreational methamphetamine use. *Drug Alcohol Rev* 2010, **29**(4):358-363.
 87. Salo R, Leamon MH, Natsuaki Y, Moore C, Waters C, Nordahl TE: Findings of preserved implicit attention in methamphetamine dependent subjects. *Prog Neuropsychopharmacol Biol Psychiatry* 2008, **32**(1):217-223.
 88. Yui K, Ishiguro T, Goto K, Ikemoto S: Precipitating factors in spontaneous recurrence of methamphetamine psychosis. *Psychopharmacology (Berl)* 1997, **134**(3):303-308.
 89. Espelin DE, Done AK: Amphetamine poisoning. Effectiveness of chlorpromazine. *N Engl J Med* 1968, **278**(25):1361-1365.
 90. Leucht S, Pitschel-Walz G, Abraham D, Kissling W: Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. *Schizophr Res* 1999, **35**(1):51-68.
 91. Shoptaw SJ, Kao U, Ling W: Treatment for amphetamine psychosis. *Cochrane Database Syst Rev* 2009, (1):CD003026.
 92. Leelahanaj T, Kongsakon R, Netrakom P: A 4-week, double-blind comparison of olanzapine with haloperidol in the treatment of amphetamine psychosis. *J Med Assoc Thai* 2005, **88**(Suppl 3):S43-S52.

93. Drake RE, Xie H, McHugo GJ, Green AI: **The effects of clozapine on alcohol and drug use disorders among patients with schizophrenia.** *Schizophr Bull* 2000, **26**(2):441–449.
94. Noordsy DL, O'Keefe C: **Effectiveness of combining atypical antipsychotics and psychosocial rehabilitation in a community mental health center setting.** *J Clin Psychiatry* 1999, **60**(Suppl 19):47–51.
95. Noordsy DL, O'Keefe C, Mueser KT, Xie H: **Six-month outcomes for patients who switched to olanzapine treatment.** *Psychiatr Serv* 2001, **52**(4):501–507.
96. Foster S, Kessel J, Berman ME, Simpson GM: **Efficacy of lorazepam and haloperidol for rapid tranquilization in a psychiatric emergency room setting.** *Int Clin Psychopharmacol* 1997, **12**(3):175–179.
97. Allen MH, Currier GW, Carpenter D, Ross RW, Docherty JP: **The expert consensus guideline series. Treatment of behavioral emergencies 2005.** *J Psychiatr Pract* 2005, **1**(11 Suppl):5–108.
98. Granado N, Ares-Santos S, Oliva I, O'Shea E, Martin ED, Colado MI, *et al*: **Dopamine D2-receptor knockout mice are protected against dopaminergic neurotoxicity induced by methamphetamine or MDMA.** *Neurobiol Dis* 2011, **42**(3):391–403.
99. Hall HV, McPherson SB, Yudko E: **Methamphetamine use - Clinical and forensic aspects.** Second Edition 2nd edition. New York: CRC Press; 2009.
100. Caton CL, Drake RE, Hasin DS, Dominguez B, Shrout PE, Samet S, *et al*: **Differences between early-phase primary psychotic disorders with concurrent substance use and substance-induced psychoses.** *Arch Gen Psychiatry* 2005, **62**(2):137–145.
101. Mathias S, Lubman DI, Hides L: **Substance-induced psychosis: a diagnostic conundrum.** *J Clin Psychiatry* 2008, **69**(3):358–367.
102. Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, *et al*: **Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review.** *Lancet* 2007, **370**(9584):319–328.
103. Zammit S, Allebeck P, Andreasson S, Lundberg I, Lewis G: **Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study.** *BMJ* 2002, **325**(7374):1199.
104. D'Souza DC, Sewell RA, Ranganathan M: **Cannabis and psychosis/ schizophrenia: human studies.** *Eur Arch Psychiatry Clin Neurosci* 2009, **259**(7):413–431.
105. Degenhardt L, Hall W, Lynskey M: **Testing hypotheses about the relationship between cannabis use and psychosis.** *Drug Alcohol Depend* 2003, **71**(1):37–48.
106. D'Souza DC: **Cannabinoids and psychosis.** *Int Rev Neurobiol* 2007, **78**:289–326.
107. Callaghan RC, Cunningham JK, Allebeck P, Arenovich T, Sajeev G, Remington G, *et al*: **Methamphetamine use and schizophrenia: a population-based cohort study in California.** *Am J Psychiatry* 2012, **169**(4):389–396.
108. Hermens DF, Lubman DI, Ward PB, Naismith SL, Hickie IB: **Amphetamine psychosis: a model for studying the onset and course of psychosis.** *Med J Aust* 2009, **190**(4 Suppl):S22–S25.

doi:10.1186/1471-244X-12-221

Cite this article as: Bramness *et al*: Amphetamine-induced psychosis - a separate diagnostic entity or primary psychosis triggered in the vulnerable?. *BMC Psychiatry* 2012 **12**:221.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit

