European Review for Medical and Pharmacological Sciences 2014; 18: 287-302

Substance abuse and psychosis. The strange case of opioids

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Abstract. – BACKGROUND: Psychoses correlated with substance abuse prove to be more common in cases involving cannabinoids, stimulants, hallucinogens, alcohol and polyabuse. Among substance abusers, it has not been ascertained whether opioids have a psychotic effect.

OBJECTIVES: The aim of this review is to investigate whether, among substances of abuse, a distinction can be drawn between pro-psychotic and anti-psychotic agents on the basis of the relationship between these substances and psychosis.

METHODS: Studies were identified by searching through multiple literature databases, including PubMed, Scopus, Web of Knowledge. Hand searches through reference lists of relevant reviews were used to complement the computer searches.

RESULTS: Looking at the relationships linking substances of abuse with psychosis, a distinction can, in fact, be drawn between pro-psychotic and anti-psychotic substances. Even if there are no differences in the addictive processes involved, opiates are the only sedative drugs that possess an anti-psychotic effect.

CONCLUSIONS: The whole topic of opiate agonism merits is due for reconsideration: it is not only the anticraving action of opiate agonism, but also its effectiveness on the psychopathological level that qualifies it as to be viewed as a powerful tool in treating mental illness.

Key Words:
Substance abuse, Psychosis, Opioid, Antipsychotic effect.

Introduction

The presence of psychotic symptoms is widespread in psychiatric disorders. Delusions and hallucinations, which are among the main symptoms of psychosis, belong to the schizophrenic spectrum. In the bipolar disorder, manic or depressive episodes, as well as mixed states, are frequently marked by psychotic symptoms. Moreover, psychosis may set in after substance abuse, often intervening with the effect of making the clinical picture indistinguishable from that of a primary psychosis. Psychosis induced by substances of abuse is most commonly developed by cannabinoids[1-7], stimulants[8-11], hallucinogens[12,13], alcohol[14-16] and polyabuse[17]. Among substance abusers, it has not yet been ascertained whether opioids exert a psychotic effect, but some authors have supported the view that opioids have antidepressant, antipanic and antipsychotic effects[18-20]. The aim of this review is to investigate the relationship between substance abuse and psychosis using as variables of interest (a) vulnerability to psychosis, (b) the development of psychosis during an intoxication or withdrawal state, (c) the clinical presentation, (d) the role of gender and (e) the neurotransmitter pathway involved. More specifically, this review intends to shed light on the various correlations between opioids and other substances of abuse in developing or acting against psychosis.

Materials and Methods

Studies were identified by searching through multiple literature databases, including PubMed, Scopus, Web of Knowledge. The key words "psychos*" "cannab*" "alcoh*" "solv*" "inhal*" "opio*" "amph*" "cocain*" "LSD" "Ketamine" "Ecstasy" "onset" "gender" "vulnerability" "intoxic*" "withdr*" "psycho*" "clinic*" "presentat*" were used in various combinations. Hand searches through reference lists of relevant reviews were used to complement the computer searches[21-26]. All our research strategies were carried out between February and December 2012.

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Cannabis and Psychosis

Clinical Presentation

Cannabis-induced psychoses were distinguished by unusual thought content, excitement, hallucinatory behaviour and uncooperativeness. The least common symptoms were anxiety, guilt feelings, depressive mood, motor retardation and blunted affect. Cognitive dysfunctions were described, too. Those with cannabis-related psychosis presented with a predominantly affective psychosis and prominent thought disorder, excitement and violence, and later presented with an improvement in symptoms if there had been abstinence from cannabis[27]. Another study similarly reported the presence of less blunted affect, more clastic aggression and violence towards others, with respect to functional psychosis[6].

Intoxication or Withdrawal Psychosis?

The relationship found in some patients between cannabis use and earlier onset of psychotic illness can now be more clearly understood[1,3,4,28-32]. A significant gradual reduction in age at the onset of psychosis was found as dependence on cannabis increased, consisting in a progressive fall in number of years for users, abusers, and dependents, with respect to non-users. For psychotic symptoms, a dose-related effect of cannabis use was seen, with vulnerable groups including individuals who used cannabis during adolescence, those who had previously experienced psychotic symptoms, and those running a high genetic risk of developing schizophrenia. Cannabis seems to be an independent risk factor, both for psychosis and for the development of psychotic symptoms[33]. In addition, studies on sibling pairs have provided further support for the hypothesis that early cannabis use is a risk-modifying factor for psychosis-related outcomes in young adults[34].

Gender

Gender did not seem to be involved in the onset of psychosis; this highlights the finding that cannabis is a dangerous, unspecific drug in young people at risk of developing psychosis[5,7,28]. It must, however, be pointed out that Arendt et al. [35] demonstrated that men who consume cannabis run a higher risk of developing psychosis than women. Their three-year study assessed a total of 535 people with a cannabis-induced psychosis, and the rates for developing schizophrenia were 47.6% in males versus 29.8% in women.

Vulnerability

Converging lines of evidence suggest that cannabinoids can produce a full range of transient schizophrenia-like positive, negative and cognitive symptoms in some healthy individuals. It is also clear that in individuals with an established psychotic disorder, cannabinoids can exacerbate symptoms, trigger relapse, and have negative consequences on the course of the illness. The mechanisms by which cannabinoids produce transient psychotic symptoms, while still unclear, may involve dopamine, GABA, and glutamate neurotransmission. A variety of factors have been proposed to mediate an individual's vulnerability to the harmful effects of the drug, one of which is their proneness to psychosis. Smoking cannabis in a naturalistic setting reliably induced marked increases in psychotomimetic symptoms. Highly psychosis-prone individuals experienced enhanced psychotomimetic states following acute cannabis use, which suggests that an individual's response to acute cannabis use and his/her psychosis-proneness scores are related, and that both may be markers of vulnerability to this drug's harmful effects[36]. Schizotypy, for instance, was associated with more frequent psychosis-like experiences and their after-effects, and high-scoring schizotypes reported more pleasurable experiences when smoking cannabis, so suggesting that cannabis use may reveal an underlying vulnerability to psychosis in those with high-scoring schizotypal traits[37,38]. Looking now at the relationship between cannabis use and psychosis, the role of affective disorders is often undervalued. Bipolar I resembles the schizoaffective disorder, in its schizo variant, and substance abuse is rather common in bipolar subjects, especially those with a chronic relapsing course, so that chronic psychosis may be an artefact of enduring substance use. The proneness to abuse shown by bipolar subjects across the whole bipolar spectrum may be a crucial link with atypical bipolar pictures involving chronic psychotic symptoms. On this view, a trait-dependent abusive behaviour of taking psychotogenic drugs may justify the independent chronicity of bipolar I subjects with comorbidity for substance abuse; if correct, this perspective would tend to assign schizoaffective disorders to the bipolar spectrum, as an extreme, atypical variant[39]. In schizophrenic patients the risk of developing cannabis dependence is six times what it is in the general population. Despite this, only a very small proportion of the general population exposed to cannabinoids de-

velop a psychotic illness. It is likely that cannabis exposure is a "component cause" that interacts with other factors to "cause" schizophrenia or a psychotic disorder, without this being either necessary or sufficient by itself to induce this result[33]. In the absence of known causes of schizophrenia, the role of component causes remains important and warrants further study. Dose, duration of exposure, and age at first exposure to cannabinoids may be important factors, along with genetic factors that interact with exposure to cannabinoids to moderate or amplify the risk of a psychotic disorder are all beginning to be elucidated[40,41]. Debates on the real chronology of the appearance of psychiatric disorders and addictive cannabis behaviour are on-going, and cannabis continues to appear as a risk factor for psychotic disorders, because it interacts with a pre-existing vulnerability[42].

Neurotransmitter Pathway Involved

While the epidemiological signal between cannabis and psychosis has gained considerable attention, the biological mechanism through which cannabis increases the risk of psychosis remains poorly understood. The endocannabinoid system plays an important role in fundamental brain developmental processes such as neuronal cell proliferation, migration and differentiation. As a result, changes in endocannabinoid activity during this specific developmental phase, induced by the psychoactive component of marijuana, Delta(9)-tetrahydrocannabinol (Δ9-THC), might lead to subtle but lasting neurobiological changes that may affect brain functions and behaviour, so increasing the risk of contracting certain neuropsychiatric diseases such as schizophrenia[43]. Animal research that has been focused on the psychotomimetic effects of cannabis[44] suggests that Δ9-THC increases dopamine levels in several regions of the brain, including the striatal and prefrontal areas. On the other hand, Cannabidiol (CBD), the main non-psychotropic component of the *Cannabis Sativa* plant, has shown therapeutic potential in several neuropsychiatric disorders[45,46]. Different types of cannabis (i.e. marijuana and hashish) have distinctive proportions of Δ9-THC and CBD. In a sample of subjects who had used the same type of cannabis on most occasions, an inverse relationship was found between CBD content and self-reported positive symptoms, but not with negative symptoms or depression; the use of cannabis with a high CBD content was associated with a significantly lower incidence of psychotic symptoms, so providing further support for the hypothesis of the antipsychotic potential of cannabidiol[47].

Amphetamines and Psychosis

Clinical Presentation

Aggressiveness and violent behaviour are the most common effects related to the use of Ecstasy, and these issues have been explored in some inquiries[48,49]. A higher level of violence seems to be present not only in active Ecstasy users, but in abstinent users, too[50]. Methamphetamine (MA) use is associated with hostility, aggression, and positive psychotic symptoms. This pattern of findings suggests that MA use leads to greater hostility by increasing positive psychotic symptoms that contribute to a perception of the environment as a hostile, threatening place as well as by increasing impulsivity. Those who had high scores for positive symptoms and impulsivity were the most hostile[51]. Regrettably, these studies often fail to reveal whether patients only used Ecstasy. Acute psychotic users showed "less blunted affect" and more "clastic aggression" and "violence towards others" than psychotic non-users, while "verbal aggression" and "self-harm behaviour" were present with equal frequency. Despite the fact that Ecstasy users take the substance in view of its supposed empathetic/entactogenic effects and to achieve a heightened sense of closeness with other people, in asymptomatic patients Ecstasy causes an opposite effect to that being sought, by increasing impulsive and violent behaviours[52]. Lastly, amphetamine use is associated with increased positive symptoms of psychosis, particularly paranoia, which contribute to a perception of the environment as a hostile, threatening place[53].

Intoxication or Withdrawal Psychosis?

Psychotic symptoms attributable to an intensive use of Ecstasy have been widely documented[9,54-61], and persecutory delusions are the most common presentation[62,63]. Psychological complications following the use of ecstasy are rare, but, when they do occur, they are really severe[64]. In some cases there is the persistence of psychopathology, even when the substance is no longer being taken[65-68]. Persistent psychosis is a common finding in heavy, chronic abusers of Ecstasy, but some authors have documented cases in which psychotic symptoms occur after a single recreational dose of Ecstasy[64,69].

Gender

There were no significant differences between men and women with regard to age, ethnicity, years of use, route of administration, or amount used in the most recent period before the onset of psychosis. During drug-use periods, women were more likely than men to report delusions of grandeur, paranoia and tactile hallucinations, while in non-use periods, women were significantly more likely than men to report the feeling that something was wrong with the way a part of their body looked, olfactory hallucinations and dressing inappropriately[70]. In reviewing the general picture, women seem more dependent on and committed to MA, but show diminished (amphetamine-stimulated) dopamine responses and a less severe degree of toxicity, as indicated by a lower incidence of emergency department-related deaths involving MA[26].

Vulnerability

Patients who have already developed psychosis are probably more inclined to experiment again with the use of amphetamines. Moreover, Ecstasy is frequently used by youngsters, in whom psychopathological symptoms will inevitably occur regardless of whether they continue to use it. The presence of a personal or family history of psychiatric disorders is important in determining the onset of psychosis[63,71], although some authors have reported cases of psychosis that occurred in individuals who had no history of psychiatric disorders or positive precedents in their family[59,66]. It must therefore be concluded that the relationship between ecstasy use and psychosis onset has not yet been clearly established. Ecstasy could directly induce psychotic symptoms or act as a trigger on susceptible individuals. The severity of psychotic symptoms, including negative ones, observed in psychotic and in schizophrenic patients taking Ecstasy is very similar[8].

Neurotransmitter Pathway Involved

MA psychosis, with rapid onset and poor prognosis, seems to be related to genetic variants of the D2 but not the D3 or D4 dopamine receptor gene[72]. As previously mentioned, amphetamine use is related to higher levels of aggression, but the underlying processes or mechanisms remain somewhat elusive. The neurotoxic pharmacological effects of amphetamine on the dopaminergic and serotonergic systems are related to aggressive, hostile behaviour in both animal and human studies. Of particular interest is the converging evidence that amphetamine use is related to the impairment of executive functions (including self-control) that are regulated by the prefrontal cortex. Taken together, these findings suggest that amphetamine users may have an impaired capacity to control or inhibit aggressive impulses. In addition, high levels of impulsivity related to amphetamine use may also play a role[53].

Cocaine and Psychosis

Clinical Presentation

In a clinical setting, it may be difficult to differentiate a cocaine-induced psychotic group from a schizophrenic one; both of these groups feel fear that individuals or organized groups may harm them in some way, but, the delusions of paranoid schizophrenic subjects are more often bizarre than those of cocaine abuse subjects. "Cocaine bugs" (parasitosis) were a perception more often found in cocaine abuse subjects. Command hallucinations were found in both groups, but in the schizophrenic group the commands perceived were more often related to harming or killing others. Cocaine abusers had a more frequent sensation of visual hallucinations, distinguished by shadows, flashing lights ("snow lights"), objects moving, and bugs crawling on their arms. The most distinctive characteristics were identity delusions, possession delusions, grandiosity delusions (besides those involving identities and possessions), and delusions in which "family members" were impostors (Capgras Syndrome) reported by paranoid schizophrenics. Cocaine abusers did not report any such delusions[73].

Intoxication or Withdrawal Psychosis?

Psychotic symptoms and experiences of paranoia and suspiciousness are reported during the use and the withdrawal of cocaine. Furthermore, although psychotic symptoms were found to be common among substance users, there was also a risk of a chronic psychotic disorder developing[9].

Gender

Among cocaine users, there were no significant differences between men and women with regard to ethnicity, years of use, route of administration, and amount used in the past week, though they differed significantly in terms of age. During a period of non-use, women were significantly more likely than men to report experiencing auditory hallucinations and tactile

hallucinations, whereas men were more likely to report delusions of grandeur. During a period of drug use, women were significantly more likely than men to report delusions of grandeur, tactile hallucinations and olfactory ones[70]. In a study that examined subjective and physiological responses to cocaine smoking, those who reported feeling paranoid/suspicious were more likely to be elderly and male[74].

Vulnerability

Experiencing transient paranoia in heavy cocaine abusers during intoxication could be the highest risk factor for developing psychosis; this danger does not exist with cocaine users who do not experience paranoia[75]. Factors underlying the development and severity of cocaine-induced psychosis (CIP) are still poorly understood [76]. To date, it has been reported that an early age of initiation of regular cocaine use occurring during vulnerable periods of brain development may lead to the increased severity of these paranoic events"[11,77]. Of course, an onset of cannabis use during adolescence can increase the risk of CIP in cocaine-dependent individuals[78] – a risk that may be present too in cases of the antisocial personality disorder [21].

Neurotransmitter Pathway Involved

Amount and duration of use are related to the development of psychosis, in which a kindling model of cocaine-induced psychosis seems to be implicated[79]. The fact that paranoia became more severe and developed more rapidly with continued drug use is consistent with a sensitization model of cocaine-induced paranoia[80,81]. In vulnerable individuals, limbic sensitization may underlie its expression, but the hypothesis of localization in a specific brain region is still speculative[75].

Hallucinogens and Psychosis

Clinical Presentation

Phencyclidine (PCP)-induced psychosis incorporates both positive (e.g. hallucinations, paranoia) and negative (e.g. emotional withdrawal, motor retardation) schizophrenic symptoms. PCP-induced psychosis also uniquely incorporates the formal thought disorder and neuropsychological deficits associated with schizophrenia. Hallucinogens are capable of producing florid psychotic states in individuals who have misused them, and it should also be noted that, when given to healthy volunteers, drug-induced paranoia, perceptual changes and a wide range of other symptoms including disorganization of thought, negativism, apathy, withdrawal, poverty of speech, perseveration and catatonic posturing[82]. In stable schizophrenic volunteers, ketamine is able to induce a dose-dependent, short-lived increase in psychotic symptoms, often reminiscent of their own acute symptoms. With regard to functional psychosis, patients taking ketamine seem to have a significantly shorter stay in hospital, and were treated more aggressively with conventional antipsychotics[13]. Comparing these kinds of symptoms with stimulant-induced psychosis, PCP-induced psychoses were less strongly associated with suspiciousness and more strongly associated with delusions of physical power, altered sensations, and unusual experiences (e.g. out of body experiences, experiencing religious figures or events directly, as in a patient's report of being "with Noah at the time of the Ark")[83]. On some occasions acute PCP psychosis in normal persons is indistinguishable from an acute episode of schizophrenia[84].

Intoxication or Withdrawal Psychosis?

Ketamine appeared to have four main effects: (1) a general depressant and/or intoxicating effect on the central nervous system; (2) perceptual alterations often referred to as 'dissociative', but not hallucinations; (3) referential ideas or delusions, plus other subjective changes in thinking; and (4) negative-type symptoms[85]. Even in healthy volunteers, ketamine induced psychotic symptoms[82]. There is a close relationship between phencyclidine (PCP) and psychosis. Low doses of PCP produce symptoms of inebriation and mild stimulation, while at higher doses it causes perceptual alteration, depersonalization and disturbances in cognition[86,87]. The psychotropic effects of ketamine range from dissociation to psychotic experiences, and include a sensation of feeling light, body distortion, absence of any sense of time, novel experiences of cosmic oneness, and out-of-body experiences. Abuse of ketamine has typically been reported in individuals who use multiple drugs, and it seems to activate significant tolerance to the substance without prominent withdrawal symptoms[88]. The most likely risk of ketamine consumption is overwhelming distress during drug action (a 'bad trip'), which could lead to potentially dangerous behaviour. Prolonged psychoses triggered by hallucinogens are less common, and, even if rare, persistent adverse reactions can occur as well[89,90].

Gender

Few studies have been dedicated to the role of gender in hallucinogen use. Some studies have shown that female rats tended to self-administer ketamine more rapidly and took more of the drug than male rats[91,92].

Vulnerability

In some individuals who have affected family members psychosis may be predictable, but the specific symptom profile may not. A placebo-controlled study on healthy individuals investigated whether individual variability in baseline physiology, as assessed using functional magnetic resonance imaging, permitted the psychosis elicited by the psychotomimetic drug ketamine to be predicted. Brain responses to cognitive task demands after a placebo had been taken predict the expression of psychotic phenomena after drug administration. Frontothalamic responses to a working memory task were associated with the tendency of subjects to experience negative symptoms when taking ketamine. Similarly, bilateral frontal responses to an attention task were predictive of negative symptoms. Frontotemporal activations during language processing tasks were predictive of thought disorders and illusory auditory experiences. A subpsychotic dose of ketamine administered during a second scanning session resulted in increased basal ganglia and thalamic activation during the working memory task, in parallel with previous reports on schizophrenic patients[93]. A personal or a family history of psychotic disorders and other severe psychiatric disorders is considered to be a risk factor for the development of psychotic symptoms during the use of ketamine[89].

Neurotransmitter Pathway Involved

The psychosis-inducing effect of ketamine provides important evidence in support of the glutamate hypothesis of schizophrenia[94-96]. The discriminative stimulus effects of LSD in rats occur in two temporal phases, with the initial effects mediated by the activation of 5-HT(2A) receptors and the later temporal phase mediated by dopamine D2-like receptors[12]. This behavioural effect is not blocked by haloperidol – a finding which supports the idea of mediation through the NMDA receptor[97]. Glutamatergic neurons are the major excitatory pathways linking the cortex, the limbic system and thalamus, regions that have been implicated in schizophrenia. The N-methyl-D-aspartic acid (NMDA) subtype of glutamate receptor may be particularly important in enacting a blockade of this receptor by the dissociative anaesthetics that reproduce in normal subjects the symptomatic manifestations of schizophrenia, including negative symptoms and cognitive impairments, while dopamine release increases in the mesolimbic system[94].

Inhalants and Psychosis

Clinical Presentation

The long-standing use of inhalants may evolve into severe psychosis resembling schizophrenia. Clinical presentations may be marked by serious disturbances, such as delusions of persecution, a bizarre delusion (e.g. that of having a five-headed snake inside one's body) and auditory hallucinations[98]. This clinical condition was shown in a young man who had no family history of schizophrenia; it was observed in the sober period when he was not under the influence of the thinner. Thus, it was difficult to diagnose this case as schizophrenia or as a flashback phenomenon due to thinner dependence[99,100]. The symptomatological characteristics of solvent-induced psychosis and schizophrenia have been comparatively studied. The two conditions did not show any differences in age of onset, nor in family history. These clinical observations lead to a very complex psychopathology, but they seem to stress the fact that the "amotivational syndrome" may be a characteristic feature of patients suffering from solvent-induced psychosis, and suggest that "solvent psychosis" should be recognized as a discernible syndrome, to be distinguished from psychotic symptoms of typical schizophrenia[101]. To better understand the effects and the damage done by inhalants, animal models have been used. Exposure to toluene in adolescence leads to social deficits and cognitive impairment in adulthood, as well as neurochemical dysfunctions in mice, which correlate with the symptoms observed in patients suffering from solvent-induced psychosis[102]. Inhalant users with or without an inhalant use disorder (IUD), according to DSM-IV criteria, had greater levels of suicidal ideation and substance use problems than non-users. Youngsters with IUDs have personal histories marked out by high levels of trauma, suicidality, psychiatric distress, antisocial behaviour and substance-related problems. A monotonic relationship between inhalant use, abuse and dependence are known to lead to serious adverse outcomes[103].

Intoxication or Withdrawal Psychosis?

Solvent-induced psychosis has been clinically identified among patients suffering from dependence on volatile solvents and those in a psychotic state as a result of chronic solvent use. Positive symptoms of schizophrenia have been reported, especially first rank symptoms, such as auditory hallucinations, and delusional perceptions, but not negative ones. Even if not in an intoxication phase, psychotic symptoms have been also been observed in a period of abstinence, in the form of a flashback phenomenon[99,100]. Besides this, by studying the symptomatological differences between solvent-induced psychosis and schizophrenia, it seems possible to recognize 'solvent psychosis' as a discernible syndrome to be distinguished from the psychotic symptoms of typical schizophrenia[101].

Gender

Using the current research methodology, no data pertinent to gender were found in the relationship between solvents and psychosis.

Vulnerability

A family history of psychiatric disorders seems to be a risk factor in the development of psychosis due to inhalants. In any case, fewer than 10% of these dependent patients had a family history of schizophrenia, and the development of inhalant-induced psychosis appeared after about 6 years of continuous use. These considerations suggest that chronic psychiatric symptoms are caused not only by inhalant abuse, but also by each patient's genetic factors, which may predispose him/her to psychosis[104].

Neurotransmitter Pathway Involved

The neuropharmacological effects of these solvents do not appear to be limited to modulation of the GABA receptor. Drug-discrimination studies using laboratory animals[105] have shown that toluene can induce subjective effects similar to those of the psychedelic anaesthetic phencyclidine (PCP), suggesting that toluene, like PCP, may block the NMDA receptor. It should be noted, however, that toluene failed to induce subjective effects similar to those of dizocilpine, another selective NMDA receptor blocker, in a similar drug-discrimination study[106]. Exposure to toluene increases dopamine levels in the rat's prefrontal cortex and striatum and increases neuronal firing in the ventral tegmental area in a manner similar to that of other drugs of abuse – effects that could be intrinsic to the rewarding effects of toluene[107,108].

Alcohol and Psychosis

Clinical Presentation

The psychotic manifestations of alcohol physical and psychiatric disorders have been well documented; however, the distinctions between the various disorders remain less well defined. Individuals often have comorbid elements belonging to several disorders, and the psychotic phenomena are often differentiated. Psychotic manifestations of alcohol withdrawal are delirium tremens[109-111], alcohol hallucinosis, Wernicke's-Korsakoff's psychosis, alcohol pellagra and hepatic encephalopathy, Marchiafava-Bignami, central pontine myelinosis and alcohol dementia[15]. It is characterized by an acute change in cognition and a disturbance of consciousness that is usually related to alcohol withdrawal but that may be associated too with the presence of a hallucinatory state[109,110,112-114]. One striking case reported was of palinacousis during alcohol hallucinosis after remission from the acoustic hallucinations that are typical of the disorder[115]. About 30% of chronic alcoholics seem to suffer from morbid jealousy, which takes various different forms. Some of the patients examined expressed it only when intoxicated, others even when sober, and in some their jealousy took the form of a delusional disorder. One conclusion to be drawn is that alcoholism appears to have an etiological role in the development of morbid jealousy[116,117].

Intoxication or Withdrawal Psychosis?

Psychotic symptoms during alcohol use may be associated either with continuous use or with a withdrawal state. Psychotic manifestations of continuous use could lead to a jealousy delusion[116,117], while delirium tremens and hallucinosis were involved in alcohol withdrawal psychosis[15,109-111].

Gender

Women had a longer duration of illness before treatment and exhibited a greater number of affective symptoms, while men were more socially isolated and had a greater number of negative symptoms. Alcohol and drug abuse appeared significantly more frequently among men. Women received comparatively more heavily medicated treatments than men[118].

Vulnerability

Only a few epidemiological findings on alcohol-induced psychotic disorder and delirium (al-

cohol-induced psychotic syndrome, AIPS) are currently available. In one inquiry on a sample of 8,028 subjects drawn from the general population of Finland, the topics chosen for investigation were the epidemiology of AIPS, the risk factors for developing AIPS among people with alcohol dependence, and mortality associated with alcohol dependence with or without AIPS. The lifetime prevalence was 0.5% for AIPS and was highest (1.8%) among men of working age. Younger age at onset of alcohol dependence, low socioeconomic status, problems with father's mental health or alcohol abuse, and multiple hospital treatments were associated with an increased risk of AIPS. Participants with a history of AIPS reported a considerable level of medical comorbidity"[14]. Some studies have shown that the major differences observed between alcoholics and controls, in terms of psychopathology, and represented by symptoms pertaining to mood, anxiety, and externalizing disorder domains, fall below the diagnostic threshold[119,120]. AIPD seems to be a discrete clinical entity that can be differentiated from schizophrenia and uncomplicated alcohol dependence; its reported features are: a significantly lower educational level, later onset of psychosis, higher levels of depressive and anxiety symptoms, fewer negative and disorganized symptoms, better insight and judgment, and less functional impairment compared with patients with schizophrenia[16]. Proneness to alcohol use has been studied at the temperamental level, where alcoholics turned out to differ significantly from controls in terms of cyclothymic traits, including a depressive component[121].

Neurotransmitter Pathway Involved

There is good evidence for a direct involvement of the cortical GABAergic system in the long-term administration of alcohol. An indirect genetic link between the GABA A receptor and schizophrenia or other psychoses has been reported. One important implication of considering GABA interneurons as playing a pivotal role in psychotic disorders like schizophrenia is the potential excitotoxicity which release from GABA inhibition might generate through increased glutamate transmission to the cortex. The profound and enduring memory impairments and the progressive enlargement of lateral ventricles that accompany chronic schizophrenia may be a consequence of GABA imbalance, which is not necessarily reversed by the anti-psychotic drugs that act on the dopamine and serotonin systems[122].

Opioid and Psychosis

Clinical Presentation

Ultrarapid opiate detoxification is a procedure that uses high doses of opiate antagonists to precipitate rapid opiate withdrawal and could develop into a psychotic episode[123]. Even if uncommon, psychosis occurring after the discontinuation of buprenorphine has been described. The clinical presentation was characterized by mystical and paranoid delusions, and intense auditory hallucinations[124].

Intoxication or Withdrawal Psychosis?

The initial hypotheses formulated on a causal link between chronic morphine intake and the onset of psychosis[125,126] were not confirmed by later studies[127,128], and most studies on the epidemiology of dual diagnosis have shown the low frequency of psychotic spectrum disorders in heroin-dependent patients, and those in methadone treatment programmes. To the best of our knowledge, no studies have been published on psychosis due to opiate intoxication. On the other hand, there have been reports in the literature on psychotic episodes related to opiate withdrawal[123]. The gradual elimination of methadone in subjects affected by previous psychotic episodes was followed by psychotic relapses[129,130]. Even if uncommon, psychosis occurring after the discontinuation of buprenorphine or other opioids has been described[124]; it usually disappeared after buprenorphine reintroduction[131].

Gender

In studies relying on the current research methodology no data pertinent to gender were found in the relationship between opiates and psychosis.

Vulnerability

In several studies the prevalence of psychotic symptoms associated with opiates, covering a spectrum going from users with no diagnosis to those with severe dependence, ranges between 6.7% and 52.2%[17,132]. A recent study on 574 patients with dual diagnosis showed a diagnosis of chronic psychosis in 15.5% of heroin-dependent patients[133]. Premorbid conditions such as temperamental assets, hyperactivity, impulsiveness, sensation-seeking, subthreshold and/or full-blown mental disorders related to mood, anxiety and impulse-control dimensions could increase vulnerability to substance use and/or progression to addiction[134]. Temperamental profile seems to play a

crucial role at the beginning of substance use. Cyclothymic, and to a lesser extent irritable traits (the 'dark side'), may represent the temperamental profile of heroin addicts, largely irrespective of comorbidity, and tend to cohere with previous conceptualizations that hypothesize "sensation-seeking" (and "novelty-seeking") as the main personality characteristics of addiction[135].

Neurotransmitter Pathway Involved

A dose of morphine blocks dopamine receptors and stimulates prolactin secretion, creating a significant elevation in basal serum prolactin[136,137]. Opiate agonists are known to induce acute neuroleptic-like effects on the endocrine system, such as hyperprolactinemia and the suppression of surrenal activity. Sedation may also take place when the tolerance threshold is exceeded during the induction phase[136,138]. On neurochemical grounds, typical antipsychotics and opiates both act on the same neuronal targets, and interfere with dopaminergic transmission, though they move along different molecular pathways[139]. Buprenorphine has shown it is active against hallucinations and delusions over a time-span of four hours in a small group of heterogeneous psychotic patients[140]. Selective k-agonist receptors (such as pentazocine), on the other hand, have psychotomimetic properties[141,142]: this toxicological property is in line with the finding that the levels of the endogenous selective k-agonist dynorphines are related to the severity of symptoms in schizophrenic subjects[143]. Opiate antagonism was also considered in relation to psychotic symptoms. For instance, naloxone administration did produce an improvement of symptoms in selected schizophrenic patients, but the results were not homogeneous[144]. Subjects who were suffering from independent psychotic disorders were more likely to drop out of naltrexone treatment by the end of the first year[145].

Discussion

The relationship between substance abuse and psychosis is far from having been completely clarified. Even if there is evidence of causal correlations between substance use and psychosis onset for most substances of abuse, this connection is less clear for opiates. Some authors have hypothesized a direct involvement of opioid neuropeptides in the pathophysiology of psychotic disorders[146]. The antipsychotic effectiveness of opiate agonists[19,147-149] is supported by the fact that methadone maintenance is responsible for the prevention of psychotic relapses in individuals who have a history of psychotic episodes. In these same subjects, the gradual elimination of methadone was followed by psychotic relapses[123,129]. This therapeutic finding is in line with the antidopaminergic activity of methadone, as documented by the increase in serum prolactin after its administration[136,137]. Moreover, the low frequency of any recurrence of psychotic episodes makes it hard to recognize schizophrenic disorders, possibly related to substance use disorders, in patients who are receiving methadone treatment[150-154]. The use of methadone has been proposed as a treatment in cases of schizophrenia that have turned out to be resistant to traditional medications, and again in cases of the early development of dyskinesia[155]. In addition, when combined with methadone, low dosages of antipsychotics such as chlorpromazine, flufenazine and haloperidol are needed to control psychotic symptoms[139,156,157]. In heroin addicts admitted to hospital for an acute psychotic episode, an increase in methadone dosage or the initiation of methadone treatment was effective in achieving control of psychotic symptoms by prescribing lower treatment dosages of antipsychotics and antimanic drugs, even when the period spent in hospital duration of hospitalization was the same[157]. The profile of psychotic heroin addicts at their first treatment attempt displays a higher level of global symptom severity, even when coupled with less severe addictive symptoms and a shorter duration of addictive history than their non-psychotic peers. We may speculate that the presence of a psychotic background underlying opiate use leads to an early worsening of global mental status through fast-acting opiate use, and may thus benefit from opiate stabilization by agonist treatment. Apart from the resolution of withdrawal-related exacerbation of psychotic symptoms, the positive impact of opiate agonism, which may have been the reason for the transition to regular heroin use, may be recovered by slow-acting, stable dose agonist treatment, but in a restabilizing form rather than a destabilizing one[158]. In other words, the long-term use of opiate agonists may be effective in treating psychotic symptoms in former psychotic patients who later became heroin addicts through a self-medication habit[158,159]. Psychotic heroin addicts may be included among those who resort to street methadone as a regular practice before entering treatment, and this decision should be regarded as a self harm-reducing behaviour rather than a

polyabuse pattern. In fact, those patients may have an independent motivation to look for treatment earlier and stay in treatment longer, which may overcome addictive ambivalence and improve compliance[160]. In the evaluation of a psychiatric diagnosis of patients entering treatment, we have tried to distinguish between patients who had started heroin use after the onset of psychiatric disorders, and those who had suffered from psychiatric disorders after the onset of their drug-using habit. Among the former, psychotic disorders and anxiety disorders were those best represented, and they were linked with a trend towards less severe addictive symptoms. The latter group mostly comprised patients suffering from mood disorders, who have more severe addictive symptoms. This time sequence does not stand as a definite proof of self-medication dynamics, but it is broadly consistent with the idea that some disorders, rather than others, may lead to heroin use in a self-medication manner[133]. The same patients would then suffer from early impairment of their psychiatric disorders, due to acquired opiate imbalance, when the severity of their addictive disease is still lower; and they will benefit more directly from the opiate-balancing effect of agonist treatment[161]. Through the recent use of an exploratory factor analysis of the 90 items in the SCL-90, a five-factor solution was identified for 1,055 heroin addicts who answered the SCL-90 questionnaire at treatment entry. These factors were named on the basis of items that showed the highest loadings. "Worthlessness and being trapped", "somatization", "sensitivity-psychoticism", "panic anxiety" and "violence-suicide" were the five dimensions that were extracted. On the basis of the highest z-scores obtained on the 5 SCL-90 factors (allowing identification of a number of dominant SCL-90 factors), subjects could be assigned to 5 mutually exclusive groups. These five groups were sufficiently distinct, and fail to reveal any significant overlap[162]. As to current knowledge, a variety of opioid medications seem to have a specific action on psychopathological symptoms. Using the SCL-90 5 factor solution, heroin-dependent patients with prominently psychopathological "sensitivity-psychoticism" characteristics showed a better level of retention in treatment when treated with methadone[163]. Methadone dosage would partially work as a psychotropic stabilizer, regardless of addictive symptoms, so that the eventual stabilization dosage is higher than in non-psychotic heroin addicts. Once both psychopathological grounds (addictive and psychotic) have been neutralized,

Table I. Substance abuse and psychosis (intentionally simplyfied).

Variables	Cannabis	Amphetamines	Cocaine	Hallucinogens	Inhalants	Alcohol	Opioids
Clinical presentation	Aggressiveness	Aggressiveness	Paranoia	Unusual experience	Bizarre delusion	Jealousy, delirium tremens, hallucinosis	Not clearly described
Intoxication or withdrawal psychosis?	Intoxication	Intoxication and withdrawal	Intoxication and withdrawal	Intoxication and withdrawal	Intoxication and withdrawal	Intoxication and withdrawal	Withdrawal
Gender	M=F (M>F?)	M=F	M=F	?	?	M≠F	?
Vulnerability	Schizotypy, genes	Family history of mental illness	Paranoicism in cocaine use	Family history of psychotic illness	Family history of psychotic illness	Presence of psychopathology	Presence of psychopathology
Neurotransmitter pathway involver	Endocannabinoid system	Dopaminergic system	Dopaminergic system	Glutamatergic system	Glutamatergic system	GABA-system	Opioidergic system

psychotic heroin addicts may meet a positive outcome, unlike what one might expect in the absence of treatment[164,165].

Conclusions

On the light of these results, substance abuse effects can be divided into those that are pro-psychotic and those that are anti-psychotic. Psychoses correlated with substance abuse prove to be more common in cases involving cannabinoids, stimulants, hallucinogens, alcohol and polyabuse. By contrast, opiates are the only sedative drugs that are marked by an anti-psychotic effect. The addictive process is the same for all substances of abuse, but that sameness does not apply to its relationship with psychosis. Thus, polyabuse can be considered as taking the initial form of an abuse of stimulants that leads to the onset of a psychosis, which, at a later stage, is complicated by opiates into an attempt to take advantage of their antipsychotic effects. We, therefore, suggest that opioid agonists deserve reconsideration, not only because of their anticraving capability, but also because of their effectiveness on the psychopathological level, which makes them a perfect tool, even in the task of curing mental illness.

Authors' declaration of personal interests

IM has served as a consultant and an advisory board member for Reckitt Benckiser Pharmaceutical; all other authors have no conflict of interest.

Declaration of funding interests

This study was supported by internal funds.

References

1) Hall W, Degenhardt L. Cannabis and the increased incidence and persistence of psychosis. Br Med J 2011; 342: d719.
2) von Limbeek J, Wouters L, Kaplan C D, Geerlings P J, von Alem V. Prevalence of psychopathology in drug-addicted Dutch. J Subst Abuse Treat 1992; 9: 43-52.
3) Kuepper R, van Os J, Lieb R, Wittchen HU, Hofler M, Henquet C. Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. Br Med J 2011; 342: d738.
4) Loga S, Loga-Zec S, Spremo M. Cannabis and psychiatric disorders. Psychiatr Danub 2010; 22: 296-297.
5) Gonzalez-Pinto A, Vega P, Ibanez B, Mosquera F, Barbeito S, Gutierrez M, Ruiz de Azua S, Ruiz I, Vieta E. Impact of cannabis and other drugs on age at onset of psychosis. J Clin Psychiatry 2008; 69: 1210-1216.
6) Maremmani I, Lazzeri A, Lovrecic M, Placidi GF, Perugi G. Diagnostic and symptomatological features in chronic psychotic patients according to cannabis use status. J Psychoactive Drugs 2004; 36: 235-241.
7) Dragt S, Nieman D H, Becker H E, van de Fliert R, Dingemans P M, de Haan L, van Amelsvoort TA, Linszen DH. Age of onset of cannabis use is associated with age of onset of high-risk symptoms for psychosis. Can J Psychiatry 2010; 55: 165-171.
8) Srisurapanont M, Arunpongpaisal 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: 959-964.
9) Karila L, Petit A, Cottencin O, Reynaud M. Methamphetamine dependence: Consequences and complications. Presse Med 2010; 39: 1246-1253.
10) Schep LJ, Slaughter RJ, Beasley DM. The clinical toxicology of metamfetamine. Clin Toxicol (Phila) 2010; 48: 675-694.
11) Floyd A G, Boutros N N, Struve F A, Wolf E, Oliwa G M. Risk factors for experiencing psychosis during cocaine use: a preliminary report. J Psychiatr Res 2006; 40: 178-182.
12) Marona-Lewicka D, Nichols CD, Nichols DE. An animal model of schizophrenia based on chronic LSD administration: Old idea, new results. Neuropharmacology 2011; 61: 503-512.
13) Carls KA, Ruehter VL. An evaluation of phencyclidine (PCP) psychosis: a retrospective analysis at a state facility. Am J Drug Alcohol Abuse 2006; 32: 673-678.
14) Perala J, Kuoppasalmi K, Pirkola S, Harkanen T, Saarni S, Tuulio-Henriksson A, Viertio S, Latvala A, Koskinen S, Lonnqvist J, Suvisaari J. Alcohol-induced psychotic disorder and delirium in the general population. Br J Psychiatry 2010; 197: 200-206.
15) Greenberg DM, Lee JW. Psychotic manifestations of alcoholism. Curr Psychiatry Rep 2001; 3: 314-318.
16) Jordaan GP, Nel DG, Hewlett RH, Emsley R. Alcohol-induced psychotic disorder: a comparative study on the clinical characteristics of patients with alcohol dependence and schizophrenia. J Stud Alcohol Drugs 2009; 70: 870-876.
17) Smith MJ, Thirthalli J, Abdallah AB, Murray RM, Cottler LB. Prevalence of psychotic symptoms in substance users: a comparison across substances. Compr Psychiatry 2009; 50: 245-250.
18) McKenna GJ. Methadone and opiate drugs: psychotropic effect and self-medication. Ann NY Acad Sci 1982; 398: 44-55.
19) Maremmani I, Pacini M, Pani PP. Effectiveness of buprenorphine in double diagnosed patients. Buprenorphine as psychothropic drug. Heroin Addict Relat Clin Probl 2006; 8: 31-48.

20) Gold MS, Pottash ALC, Sweeney DR, Martin D, Extein I. Antimanic, antidepressant, and antipanic effects of opiate: clinical, neuro-anatomical, and biochemical evidence. Ann NY Acad Sci 1982; 398: 140-150.

21) Roncero C, Daigre C, Gonzalvo B, Valero S, Castells X, Grau-Lopez L, Eiroa-Orosa FJ, Casas M. Risk factors for cocaine-induced psychosis in cocaine-dependent patients. Eur Psychiatry 2011; 28: 141-146.

22) Kolliakou A, Fusar-Poli P, Atakan Z. Cannabis abuse and vulnerability to psychosis: targeting preventive services. Curr Pharm Des 2012; 18: 542-549.

23) Ross S, Peselow E. Co-occurring psychotic and addictive disorders: neurobiology and diagnosis. Clin Neuropharmacol 2012; 35: 235-243.

24) Strobl EV, Eack SM, Swaminathan V, Visweswaran S. Predicting the risk of psychosis onset: advances and prospects. Early Interv Psychiatry 2012; 6: 368-379.

25) Fiorentini A, Volonteri LS, Dragogna F, Rovera C, Maffini M, Mauri MC, Altamura CA. Substance-induced psychoses: a critical review of the literature. Curr Drug Abuse Rev 2011; 4: 228-240.

26) Dluzen DE, Liu B. Gender differences in methamphetamine use and responses: a review. Gend Med 2008; 5: 24-35.

27) Kulhalli V, Isaac M, Murthy P. Cannabis-related psychosis: Presentation and effect of abstinence. Indian J Psychiatry 2007; 49: 256-261.

28) Barrigon ML, Gurpegui M, Ruiz-Veguilla M, Diaz FJ, Anguita M, Sarramea F, Cervilla J. Temporal relationship of first-episode non-affective psychosis with cannabis use: a clinical verification of an epidemiological hypothesis. J Psychiatr Res 2010; 44: 413-420.

29) Large M, Sharma S, Compton MT, Slade T, Nielssen O. Cannabis Use and Earlier Onset of Psychosis: A Systematic Meta-analysis. Arch Gen Psychiatry 2011; 68: 555-561.

30) Schimmelmann BG, Conus P, Cotton SM, Kupferschmid S, Karow A, Schultze-Lutter F, McGorry PD, Lambert M. Cannabis use disorder and age at onset of psychosis—a study in first-episode patients. Schizophr Res 2011; 129: 52-56.

31) Dragt S, Nieman DH, Schultze-Lutter F, van der Meer F, Becker H, de Haan L, Dingemans PM, Birchwood M, Patterson P, Salokangas RK, Heinimaa M, Heinz A, Juckel G, Graf von Reventlow H, French P, Stevens H, Ruhrmann S, Klosterkotter J, Linszen DH, group E. Cannabis use and age at onset of symptoms in subjects at clinical high risk for psychosis. Acta Psychiatr Scand 2012; 125: 45-53.

32) Compton MT, Kelley ME, Ramsay CE, Pringle M, Goulding SM, Esterberg ML, Stewart T, Walker EF. Association of pre-onset cannabis, alcohol, and tobacco use with age at onset of prodrome and age at onset of psychosis in first-episode patients. Am J Psychiatry 2009; 166: 1251-1257.

33) Semple DM, McIntosh AM, Lawrie SM. Cannabis as a risk factor for psychosis: systematic review. J Psychopharmacol 2005; 19: 187-194.

34) McGrath J, Welham J, Scott J, Varghese D, Degenhardt L, Hayatbakhsh MR, Alati R, Williams GM, Bor W, Najman JM. Association between cannabis use and psychosis-related outcomes using sibling pair analysis in a cohort of young adults. Arch Gen Psychiatry 2010; 67: 440-447.

35) Arendt M, Rosenberg R, Foldager L, Perto G, Munk-Jørgensen P. Cannabis-induced psychosis and subsequent schizophrenia-spectrum disorders: follow-up study of 535 incident cases. Br J Psychiatry 2005; 187: 510-515.

36) Mason O, Morgan CJ, Dhiman SK, Patel A, Parti N, Curran HV. Acute cannabis use causes increased psychotomimetic experiences in individuals prone to psychosis. Psychol Med 2009; 39: 951-956.

37) Barkus E, Lewis S. Schizotypy and psychosis-like experiences from recreational cannabis in a non-clinical sample. Psychol Med 2008; 38: 1267-1276.

38) Anglin DM, Corcoran CM, Brown AS, Chen H, Lighty Q, Brook JS, Cohen PR. Early cannabis use and Schizotypal Personality Disorder Symptoms from adolescence to middle adulthood. Schizophr Res 2012; 137: 45-49.

39) Pacini M, Maremmani I. Substance-Related Psychotic Chronicity and Schizoaffective Pictures: Is there a Bipolar Connection? In: Murray WH, editor. Schizoaffective Disorder: New Research. Hauppauge, NY: Nova Science Publishers; 2006. pp. 221-228.

40) D'Souza DC, Sewell RA, Ranganathan M. Cannabis and psychosis/schizophrenia: human studies. Eur Arch Psychiatry Clin Neurosci 2009; 259: 413-431.

41) Ornstein J, Stone J. Cannabis and psychosis. Br J Psychiatry 2010; 197(4): 333.

42) Vernex N, Dagher G, Touzeau D. Cannabis and Premonitory Symptoms of Schizophrenia: What Is the Time Sequence? Heroin Addict Relat Clin Probl 2009; 11: 29-34.

43) Malone DT, Hill MN, Rubino T. Adolescent cannabis use and psychosis: epidemiology and neurodevelopmental models. Br J Pharmacol 2010; 160: 511-522.

44. Kuepper R, Morrison PD, van Os J, Murray RM, Kenis G, Henquet C. Does dopamine mediate the psychosis-inducing effects of cannabis? A review and integration of findings across disciplines. Schizophr Res 2010; 121: 107-117.

45) Zuardi AW, Crippa JA, Hallak JE, Pinto JP, Chagas MH, Rodrigues GG, Dursun SM, Tumas V. Cannabidiol for the treatment of psychosis in Parkinson's disease. J Psychopharmacol 2009; 23: 979-983.

46) Marco EM, Garcia-Gutierrez MS, Bermudez-Silva FJ, Moreira FA, Guimaraes F, Manzanares J, Viveros MP. Endocannabinoid system and psychiatry: in

search of a neurobiological basis for detrimental and potential therapeutic effects. Front Behav Neurosci 2011; 5: 63.

47) Schubart CD, Sommer IE, van Gastel WA, Goetgebuer RL, Kahn RS, Boks MP. Cannabis with high cannabidiol content is associated with fewer psychotic experiences. Schizophr Res 2011; 130: 216-221.

48) Gerra G, Zaimovic A, Giusti F, Delsignore R, Raggi MA, Laviola G, Macchia T, Brambilla F. Experimentally-induced aggressive behaviour in subjects with 3,4-methylenedioxy-methanfetamine (MDMA; "Ecstasy") use hystory; psychobiological correlates. J Subst Abuse 2001; 13: 471-491.

49) Milas M. Acute psychosis with aggressive behavior as a consequence of MDMA (Ecstasy) consumption. Lijec Vjesn 2000; 122: 27-30.

50) Wan L, Baldridge RM, Colby AM, Stanford MS. Enhanced intensity dependence and aggression history indicate previous regular ecstasy use in abstinent polydrug users. Prog Neuropsychopharmacol Biol Psychiatry 2009; 33: 1484-1490.

51) Lapworth K, Dawe S, Davis P, Kavanagh D, Young R, Saunders J. Impulsivity and positive psychotic symptoms influence hostility in methamphetamine users. Addict Behav 2009; 34: 380-385.

52) Rugani F, Bacciardi S, Rovai L, Pacini M, Maremmani AGI, Deltito J, Dell'Osso L, Maremmani I. Symptomatological features of patients with and without ecstasy use during their first psychotic episode. International J Environ Res Public Health 2012; 9: 2283-2292.

53) Dawe S, Davis P, Lapworth K, McKetin R. Mechanisms underlying aggressive and hostile behavior in amphetamine users. Curr Opin Psychiatry 2009; 22: 269-273.

54) Schifano F. Chronic atypical psychosis associated with MDMA (ecstasy) abuse (letter). Lancet 1991; 338: 1335.

55) Landabaso MA, Iraurgi I, Jimenez-Lerma JM, Calle R, Sanz J, Gutierrez-Fraile M. Ecstasy-induced psychotic disorder: six-month follow-up study. Eur Addict Res 2002; 8: 133-140.

56) Vecellio M, Schopper C, Modestin J. Neuropsychiatric consequences (atypical psychosis and complex-partial seizures) of ecstasy use: possible evidence for toxicity-vulnerability predictors and implications for preventative and clinical care. J Psychopharmacol 2003; 17: 342-345.

57) Potash MN, Gordon KA, Conrad KL. Persistent Psychosis and Medical Complications After a Single Ingestion of MDMA "Ecstasy": A Case Report and Review of the Literature. Psychiatry 2009; 6: 40-44.

58) Hartel-Petri R, Rodler R, Schmeisser U, Steinmann J, Wolfersdorf M. [Increasing prevalence of amphetamine—and methamphetamine-induced psychosis]. Psychiatr Prax 2005; 32: 13-17.

59) Gouzoulis E, Borchardt D, Hermle L. A case of toxic psychosis induced by 'eve' (3,4-methylenedioxyethylam-phetamine). Arch Gen Psychiatry 1993; 50: 75.

60) Dore G, Sweeting M. Drug-induced psychosis associated with crystalline methamphetamine. Australas Psychiatry 2006; 14: 86-89.

61) McKetin R, McLaren J, Lubman DI, Hides L. The prevalence of psychotic symptoms among methamphetamine users. Addiction 2006; 101: 1473-1478.

62) McGuire P, Fahy T. Chronic paranoid psychosis after misuse of MDMA ("ecstasy"). Br Med J 1991; 302(6778): 697.

63) McGuire PK, Cope H, Fahy TA. Diversity of Psychopathology Associated with Use of 3,4-Metylendioximethamphetamine (ecstasy). Br J Psychiatry 1994; 165: 391-395.

64) Demirkiran M, Jankovic J, Dean JM. Ecstasy intoxication: an overlap between serotonin syndrome and neuroleptic malignant syndrome. Clin Neuropharmacol 1996; 19: 157-164.

65) Yui K, Goto K, Ikemoto S, Nishijima K, Yoshino T, Ishiguro T. Susceptibility to subsequent episodes of spontaneous recurrence of methamphetamine psychosis. Drug Alcohol Depend 2001; 64: 133-142.

66) Creighton F J, Black D L, Hyde C E. Ecstasy psychosis and flashbacks. Br J Psychiatry 1991; 159: 713-715.

67) Vaiva G, Bailly D, Boss V, Thomas P, Lestavel P, Goudemand M. [A case of acute psychotic episode after a single dose of ecstasy]. Encephale 2001; 27: 198-202.

68) Marchesi C, Tonna M, Maggini C. Obsessive-compulsive disorder followed by psychotic episode in long-term ecstasy misuse. World J Biol Psychiatry 2009; 10(4 Pt 2): 599-602.

69) Van Kampen J, Katz M. Persistent psychosis after a single ingestion of 'ecstasy'. Psychosomatics 2001; 42: 525-527.

70) Mahoney JJ, 3rd, Hawkins RY, De La Garza R, 2nd, Kalechstein AD, Newton T F. Relationship between gender and psychotic symptoms in cocaine-dependent and methamphetamine-dependent participants. Gend Med 2010; 7: 414-421.

71) McGuire P. Long term psychiatric and cognitive effects of MDMA use. Toxicol Lett 2000; 112-113: 153-156.

72) Ujike H, Katsu T, Okahisa Y, Takaki M, Kodama M, Inada T, Uchimura N, Yamada M, Iwata N, Sora I, Iyo M, Ozaki N, Kuroda S. Genetic variants of D2 but not D3 or D4 dopamine receptor gene are associated with rapid onset and poor prognosis of methamphetamine psychosis. Prog Neuropsychopharmacol Biol Psychiatry 2009; 33: 625-629.

73) Mitchell J, Vierkant AD. Delusions and hallucinations of cocaine abusers and paranoid schizophrenics: a comparative study. J Psychol 1991; 125: 301-310.

74) Mooney M, Sofuoglu M, Dudish-Poulsen S, Hatsukami DK. Preliminary observations of paranoia in

a human laboratory study of cocaine. Addict Behav 2006; 31: 1245-1251.

75) Satel SL, Edell WS. Cocaine-induced paranoia and psychosis proneness. Am J Psychiatry 1991; 148: 1708-1711.

76) Kuzenko N, Sareen J, Beesdo-Baum K, Perkonigg A, Hofler M, Simm J, Lieb R, Wittchen HU. Associations between use of cocaine, amphetamines, or psychedelics and psychotic symptoms in a community sample. Acta Psychiatr Scand 2011; 123: 466-474.

77) Kalayasiri R, Kranzler H R, Weiss R, Brady K, Gueorguieva R, Panhuysen C, Yang BZ, Farrer L, Gelernter J, Malison RT. Risk factors for cocaine-induced paranoia in cocaine-dependent sibling pairs. Drug Alcohol Depend. 2006; 84: 77–84.

78) Kalayasiri R, Gelernter J, Farrer L, Weiss R, Brady K, Gueorguieva R, Kranzler HR, Malison RT. Adolescent cannabis use increases risk for cocaine-induced paranoia. Drug Alcohol Depend 2010; 107: 196-201.

79) Brady KT, Lydiard RB, Malcolm R, Ballenger JC. Cocaine-induced psychosis. J Clin Psychiatry 1991; 52: 509-512.

80) Reid MS, Ciplet D, O'Leary S, Branchey M, Buydens-Branchey L, Angrist B. Sensitization to the psychosis-inducing effects of cocaine compared with measures of cocaine craving and cue reactivity. Am J Addict. 2004; 13: 305-315.

81) Cubells JF, Feinn R, Pearson D, Burda J, Tang Y, Farrer LA, Gelernter J, Kranzler H R. Rating the severity and character of transient cocaine-induced delusions and hallucinations with a new instrument, the Scale for Assessment of Positive Symptoms for Cocaine-Induced Psychosis (SAPS-CIP). Drug Alcohol Depend 2005; 80: 23-33.

82) Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 1991; 148: 1301-1308.

83) Rosse RB, Collins JP, Jr., Fay-McCarthy M, Alim TN, Wyatt RJ, Deutsch SI. Phenomenologic comparison of the idiopathic psychosis of schizophrenia and drug-induced cocaine and phencyclidine psychoses: a retrospective study. Clin Neuropharmacol 1994; 17: 359-369.

84) Erard R, Luisada PV, Peele R. The PCP psychosis: prolonged intoxication or drug-precipitated functional illness? J Psychedelic Drugs 1980; 12: 235-252.

85) Pomarol-Clotet E, Honey GD, Murray GK, Corlett PR, Absalom AR, Lee M, McKenna PJ, Bullmore E T, Fletcher PC. Psychological effects of ketamine in healthy volunteers. Phenomenological study. Br J Psychiatry 2006; 189: 173-179.

86) Pearlson GD. Psychiatric and medical syndromes associated with phencyclidine (PCP) abuse. Johns Hopkins Med J 1981; 148: 25-33.

87) Aniline O, Pitts FN. Phencyclidine: a review and perspectives. Crit Rev Toxicol 1982; 10: 145-147.

88) Pal HR, Berry N, Kumar R, Ray R. Ketamine dependence. Anaesth Intensive Care 2002; 30: 382-384.

89) Johnson M, Richards W, Griffiths R. Human hallucinogen research: guidelines for safety. J Psychopharmacol 2008; 22: 603-620.

90) Rainey J M, Crowder M K. Prolonged psychosis attributed to phencyclidine–report of 3 cases. Am J Psychiatry 1975; 132: 1076-1078.

91) Roth ME, Cosgrove KP, Carroll ME. Sex differences in the vulnerability to drug abuse: a review of preclinical studies. Neurosci Biobehav Rev 2004; 28: 533-546.

92) Zhang Y, Lu C, Zhang J, Hu L, Song H, Li J, Kang L. Gender differences in abusers of amphetamine-type stimulants and ketamine in southwestern China. Addict Behav 2012; 38: 1424-1430.

93) Honey GD, Corlett PR, Absalom AR, Lee M, Pomarol-Clotet E, Murray GK, McKenna PJ, Bullmore ET, Menon DK, Fletcher PC. Individual differences in psychotic effects of ketamine are predicted by brain function measured under placebo. J Neurosci 2008; 28: 6295-6303.

94) Goff DC, Coyle JT. The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. Am J Psychiatry 2001; 158: 1367-1377.

95) Corlett PR, Honey GD, Fletcher PC. From prediction error to psychosis: ketamine as a pharmacological model of delusions. J Psychopharmacol 2007; 21: 238-252.

96) Iasevoli F, Polese D, Ambesi-Impiombato A, Muscettola G, de Bartolomeis A. Ketamine-related expression of glutamatergic postsynaptic density genes: possible implications in psychosis. Neurosci Lett 2007; 416: 1-5.

97) Lahti A C, Koffel B, LaPorte D, Tamminga CA. Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. Neuropsychopharmacology 1995; 13: 9-19.

98) Rao NP, Gupta A, Sreejayan K, Chand PK, Benegal V, Murthy P. Toluene associated schizophrenia-like psychosis. Indian J Psychiatry 2009; 51: 329-330.

99) Saito T, Sekito Y, Ikeda N, Taniguchi E, Kadowaki I, Ashizawa T. [A case report of volatile solvent psychosis]. Nihon Arukoru Yakubutsu Igakkai Zasshi 1996; 31: 475-482.

100) Saito T, Ikeda N, Miyashita H, Yanbe K, Shirasaka T. [Clinical manifestation of volatile solvent psychosis]. Nihon Arukoru Yakubutsu Igakkai Zasshi 1997; 32: 189-196.

101) Wada K, Nakayama K, Koishikawa H, Katayama M, Hirai S, Yabana T, Aoki T, Iwashita S. Symptomatological structure of volatile solvent-induced psychosis: is "solvent psychosis" a discernible syndrome? Nihon Arukoru Yakubutsu Igakkai Zasshi 2005; 40: 471-484.

102) Lin BF, Ou MC, Chung SS, Pang CY, Chen HH. Adolescent toluene exposure produces enduring social and cognitive deficits in mice: an animal model of solvent-induced psychosis. World J Biol Psychiatry 2010; 11: 792-802.

103) Perron BE, Howard MO. Adolescent inhalant use, abuse and dependence. Addiction 2009; 104: 1185-1192.

104) Okudaira K, Yabana T, Takahashi H, Iizuka H, Nakajima K, Saito A. [Inhalant abusers and psychiatric symptoms]. Seishin Shinkeigaku Zasshi. 1996; 98: 203-212.

105) Bowen SE, Wiley JL, Jones HE, Balster RL. Phencyclidine- and diazepam-like discriminative stimulus effects of inhalants in mice. Exp Clin Psychopharmacol 1999; 7: 28-37.

106) Shelton K L, Balster R L. Effects of abused inhalants and GABA-positive modulators in dizocilpine discriminating inbred mice. Pharmacol Biochem Behav 2004; 79: 219-228.

107) Riegel AC, Zapata A, Shippenberg T S, French E D. The abused inhalant toluene increases dopamine release in the nucleus accumbens by directly stimulating ventral tegmental area neurons. Neuropsychopharmacology 2007; 32: 1558-1569.

108) Howard MO, Bowen SE, Garland EL, Perron BE, Vaughn MG. Inhalant use and inhalant use disorders in the United States. Addict Sci Clin Pract 2011; 6: 18-31.

109) Sakata S, Nakamura J. [Delirium tremens]. Ryoikibetsu Shokogun Shirizu 2003; (40): 432-436.

110) Ros LT. [Alcoholic withdrawal delirium]. Wiad Lek 1995; 48: 135-139.

111) Griffin RE, Gross GA, Teitelbaum HS. Delirium tremens: a review. J Am Osteopath Assoc 1993; 93: 924, 929-932, 935.

112) Gleason O C. Delirium. Am Fam Physician 2003; 67: 1027-1034.

113) McKeon A, Frye MA, Delanty N. The alcohol withdrawal syndrome. J Neurol Neurosurg Psychiatry 2008; 79: 854-862.

114) Yost DA. Alcohol withdrawal syndrome. Am Fam Physician. 1996; 54: 657-664, 669.

115) Wustmann T, Gutmann P. [Palinacousis in alcohol hallucinosis]. Psychiatr Prax 2007; 34: 302-304.

116) Michael A, Mirza S, Mirza KA, Babu VS, Vithayathil E. Morbid jealousy in alcoholism. Br J Psychiatry 1995; 167: 668-672.

117) Soyka M. [Alcohol hallucinosis and jealous delusion]. Fortschr Neurol Psychiatr 2006; 74: 346-352; quiz 353-344.

118) Koster A, Lajer M, Lindhardt A, Rosenbaum B. Gender differences in first episode psychosis. Soc Psychiatry Psychiatr Epidemiol 2008; 43: 940-946.

119) Fein G, Di Sclafani V, Finn P, Scheiner DL. Sub-diagnostic psychiatric comorbidity in alcoholics. Drug Alcohol Depend 2007; 87: 139-145.

120) Hulse GK, Saunders JB, Roydhouse RM, Stockwell TR, Basso MR. Screening for hazardous alcohol use and dependence in psychiatric in-patients using the AUDIT questionnaire. Drug Alcohol Rev 2000; 19: 291-298.

121) Pacini M, Maremmani I, Vitali M, Santini P, Romeo M, Ceccanti M. Affective temperaments in alcoholic patients. Alcohol 2009; 43: 397-404.

122) Keverne EB. GABA-ergic neurons and the neurobiology of schizophrenia and other psychoses. Brain Res Bull 1999; 48: 467-473.

123) Shreeram SS, McDonald T, Dennison S. Psychosis after ultrarapid opiate detoxification. Am J Psychiatry 2001; 158: 970.

124) Weibel S, Mallaret M, Bennouna-Greene M, Bertschy G. A case of acute psychosis after buprenorphine withdrawal: abrupt versus progressive discontinuation could make a difference. J clin psychiatry 2012; 73: e756.

125) Bell M. Morphine and morphinomania. N Y State Med J 1911; 93: 680-682.

126) Schwartz JM, Ksir C, Koob GF, Bloom FE. Changes in locomotor response to beta-endorphin microinfusion during and after opiate abstinence syndrome—a proposal for a model of the onset of mania. Psychiatry Res 1982; 7: 153-161.

127) Pfeffer AZ, Ruble DC. Chronic psychoses and addiction to morphine. Archives de Neurologie et Psychiatrie 1946; 56: 655-672.

128) Gerard DL, Kornetsky C. Adolescent opiate addiction: a study of control and addict sujects. Psychoanal Q 1955; 19: 457-486.

129) Levinson I, Galynker, II, Rosenthal RN. Methadone withdrawal psychosis. J Clin Psychiatry 1995; 56: 73-76.

130) Cobo J, Ramos MM, Pelaez T, Garcia G, Marsal F. Psychosis related to methadone withdrawal. Acta Neuropsychiatr 2006; 18: 50-51.

131) Karila L, Berlin I, Benyamina A, Reynaud M. Psychotic symptoms following buprenorphine withdrawal. Am J Psychiatry 2008; 165: 400-401.

132) Shoval G, Zalsman G, Nahshoni E, Weizman A. The use of illicit substances in adolescent schizophrenia inpatients. Int J Adolesc Med Health 2006; 18: 643-648.

133) Maremmani AGI, Dell'Osso L, Pacini M, Popovic D, Rovai L, Torrens M, Perugi G, Maremmani I. Dual diagnosis and chronology of illness in 1090 treatment seeking Italian heroin dependent patients. J Addict Dis 2011; 30: 123-135.

134) Pani PP, Maremmani I, Trogu E, Gessa GL, Ruiz P, Akiskal HS. Delineating the psychic structure of substance abuse and addictions: Should anxiety, mood and impulse-control dysregulation be included? J Affect Disord 2010; 122: 185-197.

135) Maremmani I, Pacini M, Popovic D, Romano A, Maremmani AG, Perugi G, Deltito J, Akiskal K, Akiskal H. Affective temperaments in heroin addiction. J Affect Disord 2009; 117: 186-192.

136) Gold MS, Redmond DE, Donabedian RK, Goodwin FK, Extein I. Increase in serum prolactin by exogenous and endogenous opiates: evidence for antidopamine and antipsychotic effects. Am J Psychiatry 1978; 135: 1415-1416.

137) Volovka SJ, Anderson B, Koz G. Naloxone and naltrexone in mental illness and tardive dyskinesia. Ann N Y Acad Sci 1982; 398: 143-152.

138) Bart G, Borg L, Schluger JH, Green M, Ho A, Kreek MJ. Suppressed prolactin response to dynorphin

A1-13 in methadone-maintained versus control subjects. J Pharmacol Exp Ther 2003; 306: 581-587.

139) Clouet DH. A biochemical and neurophysiological comparison of opioids and antipsychotics. Ann NY Acad Sci 1982; 398: 130-139.

140) Schmauss C, Yassouridis A, Emrich HM. Antipsychotic effect of buprenorphine in schizophrenia. Am J Psychiatry 1987; 144: 1340-1342.

141) Holtzman SG. Phencyclidine-like discriminative stimulus properties of psychotomimetic opioids. Ann NY Acad Sci 1982; (398): 230-239.

142) Jaffee JH, Martin WR. Opioid analgesics and antagonists. In: In Gilman AG, Rall WR, Nies AS, Taylor P, editors. Goodman and Gilmans: the pharmacological basis of therapeutics 8th ed. New York: Pergamon Press, 1990; pp. 488-521.

143) Heikkila L, Rimon R, Terenius L. Dynorphin A and substance P in the cerebrospinal fluid of schizophrenic patients. Psychiatry Res 1990; 34: 229-236.

144) Volavka J, Anderson B, Koz G. Naloxone and naltrexone in mentall illness and tardive diskynesia. Ann NY Acad Sci 1982; 398: 97-102.

145) Maremmani I, Pacini M, Giuntoli G, Lovrecic M, Perugi G. Naltrexone as maintenance therapy for heroin addiction: Predictors of response. Heroin Addict Relat Clin Probl 2004; 6: 43-52.

146) Pancheri P. La ricerca di nuove terapie antipsicotiche: i neuropeptidi. In: Reda GC, Pancheri P, editors. Terapia della schizofrenia. Roma: Il Pensiero Scientifico Ed, 1985.

147) Berger PA, Watson SJ, Akil H, Elliot GR, Rubin RT, Pfefferbaum A. Betaendorphin and schizophrenia. Arch Gen Psychiatry 1980; 37: 635-640.

148) Feinberg DT, Hartman N. Methadone and schizophrenia. Am J Psychiatry 1991; 148: 1750-1751.

149) Maremmani I, Pacini M, Lovrecic M, Lubrano S, Perugi G. Maintenance Therapy with opioid agonist for heroin addicted patients. Usefulness in the treatment of comorbid psychiatric diseases. In: Waal H, Haga E, editors. Maintenance Treatment of Heroin Addiction Evidence at the Crossroads. Oslo: Cappelen Akademisk Forlag, 2003; pp. 221-233.

150) Khantzian EJ. An ego/self theory of substance dependence: a contemporary psychoanalitic perspective. Nida Research Monograph 30. 1980: 184-191.

151) McKenna GJ. The use of methadone as a psychotropic agent. Nat Conf Methadone Treat Proc. 1973; 5: 1317-1324.

152) Mueser K T, Yarnold P R, Levinson D F, Singh H, Bellack AS, Kee K, Morrison RL, Yadalam KG. Prevalence of substance abuse in schizophrenia: Demographic and clinical correlates. Schizophr Bull 1990; 16: 31-56.

153) Resnick RB, Fink M, Freedmann AM. A cyclazocine typology in opiate dependence. Am J Psychiatry 1970; 126: 1256-1260.

154. Resnick R B, Schuyten-Resnick E, Washton A. Narchotic antagonists in the treatment of opioid dependence: review and commentary. Compr Psychiatry 1979; 20: 116-125.

155) Krausz M, Degkwitz P, Haasen C, Verthein U. Opioid addiction and suicidality. Crisis 1996; 17: 175-181.

156) Spensley J. Doxepin: A useful adjunct in the treatment of heroin addicts in a methadone program. Int J Addict 1976; 11: 191-197.

157) Pacini M, Maremmani I. Methadone reduces the need for antipsychotic and antimanic agents in heroin addicts hospitalized for manic and/or acute psychotic episodes. Heroin Addict Relat Clin Probl 2005; 7: 43-48.

158) Maremmani AGI, Bacciardi S, Rovai L, Rugani F, Dell'Osso L, Maremmani I. Natural history of addiction in psychotic heroin addicted patients at their first Agonist Opioid Treatment. Addictive Disord Their Treatment 2012; Ahead-of-print.

159) Khantzian EJ. The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. Am J Psychiatry 1985; 142: 1259-1264.

160) Maremmani I, Pacini M, Pani PP, Popovic D, Romano A, Maremmani AG, Deltito J, Perugi G. Use of street methadone in Italian heroin addicts presenting for opioid agonist treatment. J Addict Dis 2009; 28: 382-388.

161) Maremmani I, Canoniero S, Pacini M. Methadone dose and retention in treatment of heroin addicts with Bipolar I Disorder comorbidity. Preliminary Results. Heroin Addict Relat Clin Probl 2000; 2: 39-46.

162) Maremmani I, Pani PP, Pacini M, Bizzarri JV, Trogu E, Maremmani AG I, Perugi G, Gerra G, Dell'Osso L. Subtyping Patients with Heroin Addiction at Treatment Entry: Factors Derived fron the SCL-90. Ann Gen Psychiatry 2010; 9: 15.

163) Maremmani AGI, Rovai L, Pani PP, Pacini M, Lamanna F, Rugani F, Schiavi E, Dell'Osso L, Maremmani I. Do methadone and buprenorphine have the same impact on psychopathological symptoms of heroin addicts? Ann Gen Psychiatry 2011; 10: 17.

164) McLellan AT. Psychiatric severity as a predictor of outcome from substance abuse treatments. In: Meyer RE, editor. Psychopathology and Addictive Disorders. New York. Guilford Press, 1986.

165) Rounsaville BJ, Kleber HD. Psychiatric disorders in opiate addicts: preliminary findings on the cause and interaction with program type. In: Meyer R E, editor. Psychopathology and Addictive Disorders. New York: Guilford, 1986; pp. 140-168.