

Toxic Psychoses as Pharmacological Models of Schizophrenia

Stéphane Potvin^{*,1,2,3}, Emmanuel Stip^{1,3} and Jean-Yves Roy^{1,2,3}

¹Centre de recherche Fernand-Seguin; Louis-H Lafontaine Hospital, ²Clinique Cormier-Lafontaine, ³University of Montreal, Canada

Abstract: To simplify the understanding of schizophrenia, psychiatry has invested important efforts into the modelling of the disease. For obvious ethical reasons, sleep deprivation and sensory deprivation models have been rejected in the last decades. Thus, the psychotic disorders induced by psychoactive substances remain the main heuristic models of schizophrenia. Most of the work in the pharmacological modelling of schizophrenia has occurred in the sixties and seventies. Still, some observations retain their interest: 1) lasting up to six months, the amphetamine psychosis remains the best model of the *positive symptoms* of *paranoid* schizophrenia; 2) hallucinogens such as LSD or psilocybine reproduce, at best, the psychotic phenomenology observed during the first episodes of schizophrenia; 3) anesthetic dissociatives (PCP & ketamine) faithfully reproduce thought disorder, as well as the *frontal cognitive deficits* and certain *negative symptoms* of schizophrenia; 4) cannabis reproduces with fidelity the depersonalization states observed among schizophrenics; 5) alcohol hallucinosis could be the best model of the patients' hallucinations; 6) the psychotic disorder induced by muscarinic antagonists is not usually considered as a schizophrenia model, but its occurrence signals that cholinergic dysfunctions could be associated with the cognitive symptoms of the disease. As such, these observations go hand in hand with the common view of schizophrenia as a pathology of general cerebral disconnectivity that would affect a plurality of neurotransmitter systems.

Keywords: Toxic psychoses, psychoactive substances, schizophrenia, pharmacological models, neurotransmission.

TOXIC PSYCHOSES AS PHARMACOLOGICAL MODELS OF SCHIZOPHRENIA

The heterogeneity of the symptoms of schizophrenia represents a challenge to the clinician or the researcher interested in this psychological disorder. Apart from the classical positive/negative symptoms dichotomy, schizophrenia is associated with distinctive cognitive deficits, mood disturbances and motor dysfunctions.

To simplify the understanding of that complex psychopathology, psychiatry has invested important efforts into the modelling of the disease, since the beginning of the 20th century. For obvious ethical reasons, sleep deprivation and sensory deprivation models have been rejected in the last decades. Thus, the psychotic disorders induced by certain psychoactive substances remain the main heuristic models of schizophrenia. Among drugs of abuse, the psychotic disorders induced by amphetamines, cannabis, anesthetic dissociatives and alcohol still retain the attention of both clinicians and researchers. As we will see, most of the work in the pharmacological modelling of schizophrenia has occurred in the sixties and seventies. However, that work keeps influencing deeply our conceptualization of the biological bases of the psychopathology. Therefore, it appeared relevant to evaluate the strengths and the weaknesses of those pharmacological models, in the light of the current knowledge on neurotransmission.

1- Amphetamine Sensitization Model

In their acute effects, psychostimulants (amphetamines and cocaine) induce a general state of vigilance (euphoria, sustained attention, hyperactivity, etc.) that is not similar to schizophrenia. In fact, the acute effects of psychostimulants are in sharp contrast with the negative symptoms of the pathology (flat affect, anhedonia, apathy, etc.) However, after a sensitization period (increased effects for a same dose), psychostimulants can induce an authentic psychotic disorder, a phenomenon first reported by Young and Scoville in 1938 with amphetamines [1]. Following that observation, experimental studies have been undertaken in the sixties and seventies, in order to reproduce the amphetamine psychosis [2, 3]. Being successful, those studies have encouraged researchers, at the time, to espouse amphetamine psychosis as the best pharmacological model of schizophrenia.

Years later, a detailed characterization of the phenomenology of amphetamine psychosis shows that the model has both strengths and weaknesses. In general, amphetamine psychosis reproduces fairly well the positive symptoms of schizophrenia (shneiderian symptoms, paranoia, auditory hallucinations, etc.), but it mimics poorly the negative symptoms as well as the cognitive deficits associated with the disorder (Table I). Above all, amphetamine psychosis mimics closely the paranoid symptoms of schizophrenia. For instance, when methamphetamines (« ice », « crystal », etc.) are injected intravenously, they can induce a psychotic disorder lasting up to six months [4] that the clinician can easily confound with paranoid schizophrenia. However, the psychotic disorder induced by (meth) amphetamines is regularly associated with manic symptoms (hyperkinesia, sexual compulsions, etc.), whereas schizophrenia is not frequently associated with those symptoms.

*Address correspondence to this author at the Clinique Cormier-Lafontaine, 110 Prince-Arthur West, Montreal, Quebec, Canada H2X 1S7; Tel: (514) 282-6060, Ext. 417; Fax: (514) 282-5030; E-mail: stephane.potvin.ccl@ssss.gouv.qc.ca

Table 1. The Schizophrenia Symptoms Reproduced by the Psychotic Disorders Induced by Alcohol, Amphetamines, Cannabis and PCP

	Alcohol ⁵⁻⁸	Amphetamines ⁹⁻¹⁴	Cannabis ¹⁵⁻¹⁸	PCP ¹⁹⁻²¹
<i>Hallucinations</i>	Salient	Yes	Unfrequent	Yes
<i>Predominantly auditory?</i>	Yes	Yes	auditive = visual	?
<i>Paranoia</i>	Yes	Yes (severe)	Yes	Yes
<i>Systematized delusions</i>	Yes	Yes (clearly)	Yes	Not really
<i>Schneiderian symptoms</i>	Rare	Yes	Yes	?
<i>Disorganized thinking</i>	Weakly	Weakly	Weakly	Yes (clearly)
<i>Agitation</i>	Mild	Yes (severe)	Yes	Yes
<i>Hostility</i>	Yes	Yes	Mild	Yes (severe)
<i>Dissociation</i>	Mild	No	Yes (depersonalization)	Yes
<i>Negative symptoms</i>	Mild	Mild	Mild	Yes (apathy)
<i>Motor disturbances</i>	?	Extrapyramidal symptoms	Yes (motor retardation)	?
<i>Maximal length</i>	A few months?	6 months	A few weeks	A few weeks
<i>In vulnerable subjects only?</i>	No?	No	Yes	No
<i>Differences</i>	1) visual hallucinations	1) visual & tactile hallucinations 2) compulsive sexuality	1) visual hallucinations 2) panic attacks	1) visual hallucinations 2) delusions of physical power

Coupled with the fact the antipsychotic drugs share a common antagonist action at the dopamine D₂ receptors [22], the observation of an amphetamine psychosis has paved the way to the dopaminergic hypothesis of schizophrenia. According to the hypothesis, schizophrenia would be characterized by a general dopaminergic dysfunction of the mesocorticolimbic system [23]. In rodents, the acute administration of amphetamines increases dopamine release in the mesolimbic reward system, whose dopaminergic neurons project from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) [24]. After a sensitization period to the effects of amphetamines, a *hyperdopaminergic* state is observed in the brain reward system, that would be secondary to a *hypodopaminergic* state in the mesocortical system, whose neurons project from the VTA to the (medial) prefrontal cortex (Fig. 1). Following those observations from basic science, it was hypothesized that the mesocortical hypodopaminergic state would underscore the negative symptoms and the frontal cognitive deficits of schizophrenia, whereas the mesolimbic *hyperdopaminergic* would be associated with the positive symptoms.

Since then, both experimental and neurochemical data have confirmed the second part of the dopaminergic hypothesis. First of all, studies in the laboratory have been undertaken in the sixties, seventies and eighties, showing that the experimental administration of sub-psychogenic doses of amphetamines induces a psychotic relapse among 40 % of schizophrenia patients [26]. Following those clinical results, studies have been carried in the beginning of the nineties in order to assess the *in vivo* functioning of dopamine in the schizophrenia brain. Using both positron emission tomography (PET) and single-photon emission computed tomography (SPECT), researchers have targeted the binding of radiotracers like raclopride (PET) and IBZM (SPECT) to the D₂ receptors, in response to the administration of amphetamines. Using those procedures, the scientific community has been able to demonstrate that the striatal release of dopamine (eg. the decrease in the binding of D₂ receptors) is almost two times superior among schizophrenics, compared to healthy volunteers, mainly when patients are experiencing the acute phase of psychosis [27, 28]. Neuroimaging researchers were therefore confirming what clinicians were suspecting since decades, namely that

the dopaminergic hypothesis seems to chiefly explain the positive symptoms of schizophrenia.

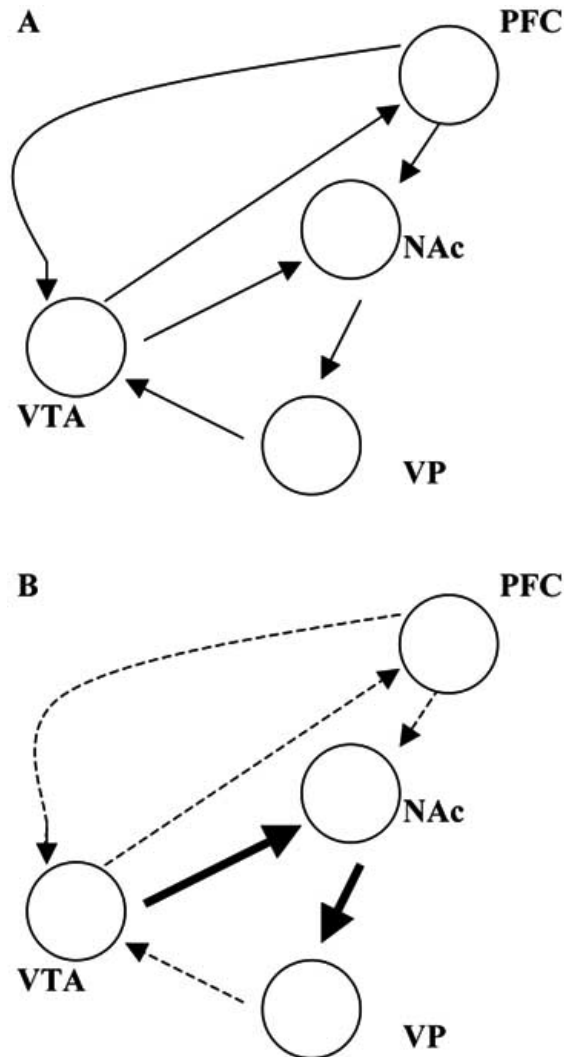


Fig. (1). Mesocorticolimbic dysfunctions induced after amphetamine sensitization.

A: Normal functioning of the mesocorticolimbic system. Dopaminergic neurons project from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) (*reward system*) and to the prefrontal cortex (PFC) (*mesocortical system*). Glutamatergic neurons project from the PFC to the NAc and the VTA. GABAergic neurons project from the NAc to the ventral pallidum (VP), and from the VP to the VTA.

B: The mesocorticolimbic system after amphetamine sensitization. A hypodopaminergic state is observed in the mesocortical system. Glutamatergic and GABAergic systems collapse. The reward system is therefore disinhibited [25].

Regarding the notion that a mesocortical hypodopaminergic state would underscore the negative and the cognitive symptoms of schizophrenia, data collected so far are less convincing. In rats, the acute administration of amphetamines is known to increase dopamine release in the (medial) prefrontal cortex. Accordingly, experimental studies show that the administration of amphetamines in laboratory partially relieves the negative symptoms of schizophrenia [29]. In addition, recent results from brain imaging studies

show that the D_1 receptors are up regulated in the dorsolateral prefrontal cortex (DLPFC) of schizophrenics. That up regulation is thought to reflect a neuroadaptation to a decreased dopaminergic activity. Interestingly, the up regulation of D_1 receptors in the DLPFC seems to be negatively correlated to the performance of patients on a working memory task [30]. Finally, genetic studies suggest that there would be an association between the COMT (catechol-O-methyltransferase) gene polymorphism and the frontal cognitive deficits of schizophrenia. COMT is a catabolic enzyme of catecholamines (dopamine & norepinephrine), mainly localized in the prefrontal cortex. However, a recent meta-analysis shows that the suspected association between the COMT gene polymorphism and the cognitive deficits of schizophrenia would be modest, at best [31].

1.1. Scope of the Amphetamine Psychosis Model

Up to now, the global function of dopamine in the brain remains a matter of debate. In 1985, Wise hypothesized that dopamine was involved in the hedonic component of reward [32]. Since then, it has been demonstrated, in animals, that the firing of dopamine neurons show a habituation to reward consumption, but not to the anticipation of reward. In addition, it appears that dopamine also responds to aversive stimuli, like stress [33]. Thus, a majority of researchers prefer to think, like Robinson and Berridge [34], that dopamine would be involved in the *motivational*, but not the *hedonic*, component of reward. The global function of dopamine would be to signal the “motivational salience” of environmental stimuli that are necessary to our survival. Following that functional hypothesis, one could expect that after a sensitization period, dopamine would confer motivational salience, in a chaotic way, to stimuli with no or little biological significance. According to Kapur [35], psychosis would correspond to a cognitive construction, elaborated from aberrant salient informations.

The scope of the amphetamine sensitization model is not restricted to the understanding of the positive symptomatology of schizophrenia. The model also seems to be relevant to the understanding of the biological underpinnings of the 47 % lifetime prevalence of substance use disorders among schizophrenia patients [36]. Indeed, most drugs of abuse increase dopamine release in the brain reward system, both in animals and in humans [37]. When amphetamine sensitization occurs, a *hyperdopaminergic* state is observed in that very system [25]. If psychosis corresponds to a state of endogenous sensitization, then, schizophrenia patients should be vulnerable to the rewarding properties of psychoactive substances.

The amphetamine sensitization model is also useful to the validation of more complex animal models of schizophrenia, such as the neonatal ventral hippocampus lesion (NVHL) model, developed by Lipska and Weinberger in 1993 [38]. When rats are neonatally lesioned to the ventral hippocampus, lesioned rodents show, once adult, an increased responsiveness to the locomotor effects of amphetamines. Furthermore, recent studies demonstrate, more specifically, that lesioned rodents are more prone to self-administer cocaine, compared to sham rodents [39]. Those results tend to support the idea that patients with

schizophrenia would be vulnerable to the rewarding effects of drugs of abuse.

However fruitful, the amphetamine psychosis model does not constitute, *per se*, a model of schizophrenia, but rather represents a model of the *positive symptoms* of the disorder. Because of their transient nature, the positive symptoms do not form the core symptoms of the disease. In that respect, longitudinal studies show that the negative symptoms and the cognitive deficits are more stable in time. In addition, they are better precursors of the psychopathology, and they are better predictors of social integration [40]. Still, the dopaminergic hypothesis, historically derived from the observation of the amphetamine psychosis, remains up to now the most robust pathophysiological hypothesis of schizophrenia. But genetic studies targeting the dopaminergic system among schizophrenics have failed to produce positive results, even though those studies have targeted the dopamine receptors, the dopamine transporters, as well as the metabolic enzymes of dopamine [41]. Still, a recent meta-analysis of the studies assessing the D₂ receptor gene (DRD2) has shown that the odds ratio of the frequency of the DRD2 Cys311 Ser allele is 1.3 ($p = 0.007$) among schizophrenia patients, compared to healthy volunteers [42]. Among the dopaminergic receptors, D₄ has also attracted interest from researchers, although to a lesser extent. An involvement of D₄ in the pathophysiology of schizophrenia has been suspected based on the neuropharmacology of clozapine. It was hypothesized that clozapine's superior efficacy in refractory schizophrenia [43] would depend on its greater affinity for D₄ than for D₂ [44]. However, the selective D₄ antagonist sonepiprazole has been tested recently in a double-blind placebo-controlled clinical trial, with no efficacy [45].

2- The Rise and Fall of the LSD Model

Since the beginning of the 20th century, researchers have been struck by the similarities between the pharmacological effects of hallucinogens and the psychotic phenomenology, especially schizophrenia. Already in 1940, Stockings initiated experimental studies, where mescaline was administered to healthy volunteers in order to characterize the effects produced by the substance [46]. Mescaline is chemically similar to amphetamines – a fact that Stockings could not be aware of –, even though they differ in their pharmacodynamic mechanisms of action, as we will see.

In the sixties and seventies, research intensifies, inspired by the hippie movement. On that basis, an increasing number of authors show an interest in the psychedelic model of psychosis. But now, research focuses on LSD (lysergic acid diethylamide) as an experimental model, not on mescaline anymore. Despite the efforts invested, research in the domain has led to a rejection of LSD as a pharmacological model of schizophrenia, because of five main weaknesses, anticipated in great part by Hollister already in the beginning of the sixties [47]:

- Hallucinogens do not produce a real disorganization of thinking;
- they induce only mild negative symptoms;
- They do not induce real delusions;

- They produce psychedelic effects that are not frequently observed among schizophrenia patients (example: synesthesia);
- Lastly, they engender, in their acute effects, *perceptual distortions*, not frank hallucinations. Indeed, those distortions are not mistaken with the reality. Furthermore, those distortions are mainly *visual*, not auditory.

More than forty years later, it appears that the critics first addressed by Hollister to the psychedelic model keep their general validity [48, 49]. Despite those limits, the psychedelic model is currently the center of a renewed interest. Authors working in that domain are conscious that the validity of the model is probably limited to the modelling of the first episodes of schizophrenia, which are associated with psychedelic experiences [50]. In support of the model, hallucinogens can induce, under particular circumstances, toxic psychoses that can be associated with authentic hallucinations (mainly *visual*, again). In addition, hallucinogens would be *agonists* at the 5-HT_{2a} serotonin receptor, precisely the receptor on which atypical antipsychotic drugs exert an *antagonist* action [51]. Most *post mortem* studies suggest that the number of 5-HT₂ receptors would be diminished in the prefrontal cortex of schizophrenia patients. But the only *in vivo* study undertaken so far did not confirm that observation [52]. Without being directly involved in the pathophysiology of schizophrenia, the 5-HT_{2a} receptors could still play a modulatory role in antipsychotic therapeutics. In animals, serotonin and dopamine have opposing effects. For instance, it is established that selective serotonin reuptake inhibitors (SSRI) and 5-HT_{2a} receptor agonists inhibit dopamine release in the basal ganglia. Conversely, 5-HT_{2a} antagonists stimulate dopamine release in the basal ganglia and more importantly, in the prefrontal cortex. As mentioned previously, a dopaminergic hypoactivity seems to be associated with the negative and cognitive symptoms of schizophrenia. Because of their 5-HT_{2a} antagonism, atypical antipsychotic drugs disinhibit dopaminergic neurons in the prefrontal cortex. Thus, their presumed positive impact on negative and cognitive symptoms [53]. Meta-analytic studies have provided partial support to the hypothesis of a greater efficacy of atypical antipsychotic drugs in the treatment of those symptoms [54, 55, 56]. Also, preliminary evidence from human imaging studies suggest that atypical antipsychotics would (partially) restore prefrontal activity in schizophrenia [57, 58]. Further, SR46349B, a 5-HT_{2a/2c} antagonist, has been recently investigated as a monotherapy in schizophrenia in a double-blind study, and it has shown efficacy against depressive, but also negative symptoms [59]. However, a meta-analysis has demonstrated that the antipsychotic amisulpride, a selective D₂/D₃ antagonist, has a greater efficacy against negative symptoms compared to conventional antipsychotic drugs, despite its lack of affinity for 5-HT_{2a} [60].

In the end, the link between serotonin and schizophrenia appears paradoxical. While the LSD model of schizophrenia seems to mimic the psychedelic experiences associated with the first episodes of psychosis, the study of the pharmacological mechanisms of action of atypical antipsychotics suggests a modulatory role of serotonin in the negative (and cognitive) symptoms.

2.1. The Dissociative Model

Around the end of the fifties, the scientific community becomes aware that phencyclidine (PCP), a medication prescribed in general anesthesia, has nocive effects. After anesthesia, an important number of patients treated with PCP experience psychotic phenomenons. The phenomenology of PCP psychosis is highly unpredictable. The mood of patients can vary from apathy to aggressivity or violence. Their thinking is disorganized. They experience dissociative symptoms. The perception of their body is markedly impaired. Some consumers have the impression that they can fly. Moreover, patients report hallucinations, and they can become quite paranoid. However, PCP psychosis does not seem to reproduce the different types of delusions associated with schizophrenia (Table I), apart from paranoia.

Those first observations are rapidly forgotten, since the mechanism of action remains unknown at the time. In 1979, with discovery of the PCP site inside the ion channel of the *N-methyl-D-aspartate* (NMDA) receptor of glutamate [61], the scientific community begins to seriously re-consider the PCP psychosis as a potential and promising model of schizophrenia. That regained interest towards anesthetic dissociatives paves the way, in the nineties, to the experimental studies assessing the psychological impact of the administration of ketamine to healthy volunteers, since ketamine is a synthetic derivative less toxic than PCP. In those studies carried in the laboratory, ketamine is shown to induce, at sub-anesthetic doses, pharmacological effects similar to the schizophrenia phenomenology [62, 63, 64, 65]. First of all, ketamine produces dissociative states (depersonalization, derealization, etc.). In addition, it alters cognition and thought in a fashion similar to what is observed among schizophrenics. Research establishes that ketamine disorganizes thought, that it impairs abstract thinking and attentional vigilance, and that it engenders perseverative errors. Under ketamine, the thinking of subjects becomes incoherent and tangential. In sum, ketamine reproduces, among healthy volunteers, the frontal cognitive deficits typical of schizophrenia. Lastly, ketamine engenders emotional blunting and social withdrawal. It therefore seems to represent a better model of the negative symptoms of schizophrenia than the amphetamine psychosis.

Challenge studies with ketamine have elicited enthusiasm. However, some researchers doubt that anesthetic dissociatives can closely mimic the positive symptoms of schizophrenia [66]. Indeed, anesthetic dissociatives generally induce pseudo-delusions, not frank delusions, apart from paranoia. Further, at sub-anesthetic doses, ketamine produces *visual illusions*, not *auditory hallucinations*.

Thus, it appears that the anesthetic dissociatives mainly model the frontal cognitive deficits and certain negative symptoms of schizophrenia. Since PCP and ketamine are NMDA antagonists, the previous observations suggest that the glutamatergic hypothesis of schizophrenia [67] would chiefly explain those symptoms. If true, that hypothesis would have consequences on the pharmacological treatment of schizophrenia. However, the clinical studies carried so far in that perspective has lead to only modest results. Indeed,

glycine (a NMDA co-agonist), D-cycloserine (a partial agonist at the glycine site of the NMDA receptor), and D-serine (an agonist at the NMDA glycine site) have all been investigated among schizophrenia patients, in double-blind studies, as adjunctive medications. Generally, those studies suggest that the facilitation of glutamatergic activity via the NMDA receptor offers, at best, a partial relief of the negative and/or cognitive symptoms of schizophrenia [68].

On the pathophysiological level, the conclusions that can be reached regarding the PCP psychosis remain uncertain. At first glance, the observation of a PCP psychosis and the challenge studies with ketamine suggest that schizophrenia would be associated with NMDA receptor alterations. But the complexity of the neuropharmacology of PCP and ketamine confounds such an inference. Apart from being NMDA antagonists, PCP and ketamine are also dopamine and serotonin re-uptake inhibitors. Further, they have an affinity for D₂ and 5-HT₂ receptors similar to their affinity for NMDA receptors, and they seem to act as partial D₂ agonists [69]. Also of concern, the studies in brain imaging have shown that the most prominent alterations observed in schizophrenia affect the AMPA (amino-methyl-propionic acid) receptors, not the NMDA receptors, of glutamate [70].

3- The Cannabinoid Model

The idea of a link between the effects of cannabis and mental health, especially psychosis, is not a novel one. It can be traced back to the work of Moreau de Tours in the 19th century [71]. In its acute effects, cannabis can produce, among healthy volunteers, effects similar to the psychosis phenomenology in general, and schizophrenia in particular. For once, cannabis impairs short-term working memory [72], a cognitive function disturbed among schizophrenics. Moreover, cannabis produces perceptual illusions (binocular depth inversion paradigm) similar to those observed among patients with schizophrenia [73]. At certain doses, cannabis can also induce depersonalization states [74], a symptom more frequently present in schizophrenia than usually thought.

Among consumers who show a psychotic vulnerability (example: schizotypic traits), cannabis can induce, in rare occasions, transient toxic psychoses that mimic the schizophrenia phenomenology (Table I). The psychotic disorder induced by cannabis is characterized by depersonalization, paranoia and delusions (such as grandiosity). Hallucinations are not frequent, and they occur in both visual and auditory modalities. Thinking is partially disorganized, and the negative symptoms are only of mild intensity (example: flat affect). Based on those similarities and differences, the diagnostic statue of the cannabis-induced psychotic disorder remains the topic of a debate among clinicians, who are still unable to determine whether the cannabinoid psychosis is a diagnostic entity distinct from the endogenous psychoses, including schizophrenia [75, 76].

In its chronic effects, cannabis can provoke an amotivational syndrome that mimics closely the negative symptoms of schizophrenia, especially anhedonia. But it remains to be proved that the syndrome is the direct product of the long-term effects of cannabis, not the product of the idleness of counter-culture [77].

Naturalistic studies carried among regular consumers show that there is a relationship between cannabis intake and schizotypy [78, 79]. In general, the more a subject consumes regularly cannabis, the more he will show a group of traits typically associated with schizophrenia, such as perceptual aberrations, anhedonia, magical thinking and social withdrawal. Relying on correlational statistics, those studies do not allow to conclude, however, if the schizotypic traits observed are primary or secondary to cannabis intake. It remains possible, indeed, that those subjects would be predisposed to smoke cannabis, because their personality would be marked by premorbid schizotypic traits.

The odds ratio that schizophrenia patients will develop a cannabis use disorder (abuse/dependence) is six times higher than the relative risk of the general population [36]. Still, the reasons that motivate schizophrenics to consume cannabis remain unclear. Prospective research indicates that the frequency of psychotic relapses and hospitalizations is increased among the schizophrenia patients who use cannabis, compared to those who are abstinent [80]. Since the publication of the classic populational study of

Andreasson of 1987 [81], it is further suspected that chronic cannabis smoking would also increase the *incidence* of schizophrenia. Carried among 45 570 Swedish conscripts, the study showed that heavy cannabis smoking was associated with an increased risk for schizophrenia (2.9 times). But the study had methodological flaws [82]: 1) the consumption of other psychomimetic drugs was not documented; 2) schizophrenia diagnosis were based on medical files; 3) premorbid personality traits were not controlled. Since then, studies of better methodological quality have been published, and they hardly confirmed Andreasson's hypothesis (Table II). While one study has validated the postulated link between schizophrenia and cannabis smoking [83], three other studies showed that chronic cannabis smoking increased the incidence of *psychotic symptoms* in schizophrenia without increasing the incidence of *schizophrenia diagnoses* [84, 85, 86]. Moreover, two other studies have produced negative results [87, 88].

Apart from those clinical and experimental observations, neuroscientific data seem to support the idea of a kinship

Table 2. Cannabis Consumption as a Risk Factor for Schizophrenia

Authors	Type of study	Population	Control(s)	Results
Allebeck <i>et al.</i> 1993 [89]	Prospective & longitudinal *	229 cannabis -dependent psychotic subjects		Cannabis smoking precedes the first psychotic symptoms in 69 % of cases
Andreasson <i>et al.</i> 1989 [90]	Prospective & longitudinal *	45 570 Swedish military conscripts	Other drugs	Cannabis smoking → higher risk for schizophrenia
Andreasson <i>et al.</i> 1987 [81]	Prospective & longitudinal (15 years)	45 570 Swedish military conscripts		Heavy cannabis smoking → higher risk for schizophrenia (2.9 times)
Arseneault <i>et al.</i> 2002 [84]	Prospective & longitudinal	Cohort of 759 new-borns (0 – 26 years)	Psychotic symptoms preceding cannabis smoking	Cannabis smoking → more psychotic symptoms, but not more psychosis diagnoses
Degenhardt <i>et al.</i> 2003 [87]	Prospective & longitudinal	8 cohorts of new borns (Australia)		Cannabis smoking does not increase schizophrenia incidence
Fergusson <i>et al.</i> 2003 [85]	Prospective & longitudinal	Cohort of 1265 new-borns (0 – 21 ans)		Cannabis dependence → more frequent psychotic symptoms (1.8 times)
Kwapil <i>et al.</i> 1996 [91]	Prospective & longitudinal (10 years)	534 étudiants universitaires	Other drugs	Schizotypy predicts later cannabis smoking
Phillips <i>et al.</i> 2002 [88]	Prospective & longitudinal (12 months)	100 « high-risk » psychosis subjects	Other drugs / anti-psychotics	Past cannabis smoking does not increase risk for psychosis
Tien <i>et al.</i> 1990 [86]	Epidemiology (12 months)	4994 adults		Cannabis smoking → more psychotic experiences (2 times)
Van Os <i>et al.</i> 2002 [83]	Prospective & longitudinal (3 years)	4045 healthy volunteers 59 psychotics		Cannabis smoking → increased risk for psychosis
Zammit <i>et al.</i> 2002 [92]	Prospective & longitudinal *	45 570 Swedish military conscripts	Premorbid personality traits	Cannabis smoking → higher risk for schizophrenia

*Follow-up of Andreasson *et al.* 1987.

between cannabinoid pharmacology and the pathophysiology of schizophrenia. First, a reduction in the P300 evoked potentials is observed among chronic cannabis consumers, analog to the reduction that has regularly been reported among schizophrenics [93]. Moreover, the endogenous cannabinoid system, composed of at least three natural ligands (anandamide, palmitylethanolamide and oleylethanolamide) and at least two receptors (CB₁ and CB₂), is localized in brain regions known to be impaired in schizophrenia, such as the prefrontal cortex, the hippocampus, and the basal ganglia [94]. The endocannabinoid levels (namely anandamide), measured in the cerebrospinal fluid, are abnormally elevated among schizophrenia patients [95]. Using positron emission tomography (PET), a *post mortem* study shows that the CB₁ receptor density is altered in the dorsolateral prefrontal cortex of schizophrenics [96]. Lastly, there would be an association between CB₁ receptor gene polymorphism and schizophrenia [97]. Taken together, those results fit with the gain in popularity of cannabis as an experimental model of schizophrenia [98]. However, the CB₁ antagonist rimonabant has been investigated in schizophrenia, with no success [59]. As an alternative, cannabidiol is currently under investigation in schizophrenia. A natural compound of marijuana, cannabidiol acts as a CB₁ antagonist and also as an inhibitor of the anandamide transporter. Case reports suggest its efficacy in the treatment of psychosis [99].

4- Alcohol hallucinosis

In the history of the pharmacological modelling of schizophrenia, alcohol psychosis has always been singular. Being proposed as a schizophrenia model decades ago, alcohol psychosis has remained unpopular since then, possibly because alcohol can only induce a psychotic disorder among patients who have abused the substance for many years. In its acute effects (anxiolysis, analgesia, disinhibition, etc.), alcohol does not mimic at all the schizophrenia phenomenology. However, among consumers generally older than forty years old, alcohol can induce, mainly during withdrawal, psychotic symptoms. In those circumstances, alcohol can provoke two types of psychoses: *delirium tremens* and *alcohol hallucinosis*, which can be hard to differentiate from one another. *Delirium tremens* usually occurs a few days after the beginning of abstinence. The sensorium of patients is altered, hallucinations are salient and mainly *visual* (example: animals), delusions are not systematized, and agitation as well as anxiety symptoms are quite severe. During alcohol hallucinosis, which generally occurs following *delirium tremens*, the patients' sensorium regains normalcy, their hallucinations, still salient, are now mainly *auditive* (example: voices), delusions are now systematized, and anxiety remains severe (Table I).

Difficult to differentiate from *delirium tremens*, alcohol hallucinosis can easily be mistaken with schizophrenia. Even though alcohol hallucinosis is rarely mentioned as a schizophrenia model, a careful examination of its phenomenology leads to think that it could represent an excellent model of the *hallucinations* of schizophrenia. However, it must be reminded that alcohol hallucinosis occurs after many years of consumption. Furthermore, it is

hard to identify the neurotransmitters by which alcohol would produce hallucinations, since ethanol exerts a modulatory action on many neurotransmitters, namely GABA (gamma-aminobutyric acid), glutamate, dopamine, serotonin, the endogenous opioids [100], as well as the endogenous cannabinoids [101]. Interestingly, brain imaging case reports carried among patients suffering from alcohol hallucinosis does not reveal dopaminergic disturbances, but decreased frontal and thalamic functioning [102, 103]. Thus, the alcohol hallucinosis model does not seem to be compatible with the amphetamine sensitization model.

5- The Cholinergic Hypothesis

Historically, antagonists of the muscarinic receptors of acetylcholine (like atropine and scopolamine) have been used in the treatment of Parkinson's disease and of the extrapyramidal signs induced by neuroleptics, before it was discovered that those medications increase dopamine release in the basal ganglia. Exerting a pro-dopaminergic action, anticholinergics are sometimes abused as street drugs. At weak doses, those psychoactive substances relieve parkinsonian signs, but at higher doses, they produce euphoric effects as well as perceptual and cognitive distortions. Even if the phenomenon has not been reported regularly in the literature, anticholinergics can provoke delusions and hallucinations among healthy volunteers [104]. The psychotic disorder induced by anticholinergic drugs is usually not considered as a schizophrenia model. But its occurrence suggests that the psychopathology could be associated with cholinergic dysfunctions, notably affecting cognition. Some data give support to that hypothesis. First, neuropsychological research identifies, among elder schizophrenics, cognitive dysfunctions similar to those observed among patients suffering from Alzheimer's disease [105], a disease associated with cholinergic impairments. Moreover, muscarinic antagonists, which are prescribed to treat the extrapyramidal symptoms of schizophrenia patients, are known to exert a negative impact on the cognition of those patients. Inversely, preliminary data suggests that medications increasing cholinergic activity would improve the cognitive functions of schizophrenics. It would be the case of the inhibitors of acetylcholinesterase, the enzyme that degrades acetylcholine [106]. Following that line of thought, the beneficial impact of clozapine and olanzapine has been attributed to their muscarinic activity: not only do these atypical antipsychotic drugs possess a noticeable affinity for muscarinic receptors, but they also seem to act as partial agonists at the M₄ muscarinic receptor [107]. Further strengthening the association between schizophrenia and acetylcholine, clinical studies show that 80 to 90 % of patients with schizophrenia consume tobacco, whose main psychoactive substance, nicotine, is an agonist at nicotinic cholinergic receptors. Clinical research demonstrates that tobacco smoking seems to improve the attentional vigilance, to relieve the anhedonia, and to diminish the intensity of the parkinsonian symptoms of schizophrenia [108]. More precisely, experimental studies show that nicotine normalizes the auditory sensory gating deficits of schizophrenics and of their relatives. Lastly, linkage analyses involve the locus q14, located on the chromosome 15, in the auditory gating deficits of

schizophrenia patients. Of interest, that locus corresponds to the localization of the gene coding for the α_7 nicotinic receptor of acetylcholine, a receptor deeply expressed in the hippocampus [109]. Accordingly, *post mortem* studies show that the number of nicotinic receptors is diminished in the hippocampus of schizophrenics [110].

6- Heterogenous Models for a Heterogenous Disorder

The brief historical overview of the pharmacological models of schizophrenia leads to two general conclusions. The first one is that psychoactive substances provoke, most of the time, delusional disorders or hallucinoses, but less frequently frank psychoses. The second one, and also the most important, is that schizophrenia can not be easily explained by reductionist models. Most drugs of abuse can induce manifestations associated with the psychopathology, but none of them actually reproduces schizophrenia in its integral phenomenology.

Still, some observations keep their interest: 1) Lasting up to six months, the amphetamine psychosis remains the best model of the *positive symptoms* of *paranoid* schizophrenia; 2) Hallucinogens such as LSD or psilocybine reproduce, at best, the psychotic phenomenology observed during the first episodes of schizophrenia; 3) Anesthetic dissociatives (PCP & ketamine) faithfully reproduce thought disorder, as well as the *frontal cognitive deficits* and certain *negative symptoms* of schizophrenia; 4) Cannabis reproduces with fidelity the depersonalization states observed among schizophrenics. Neurobiological data suggest, however, that the cannabis – schizophrenia link would be closer; 5) Hallucinogens (including cannabis, LSD and PCP) might be better models of dissociative disorders than of schizophrenia; 6) Since alcohol hallucinosis is associated with salient hallucinations, predominantly *auditive*, it could be the best model of the patients' hallucinations. We still ignore, however, what neurotransmitter(s) could relay these hallucinations in the brain; 7) The psychotic disorder induced by muscarinic antagonists is not usually considered as a schizophrenia model, but its occurrence signals that cholinergic dysfunctions could be associated with the cognitive symptoms of the disease; 8) The toxic psychoses induced by alcohol, amphetamines, cannabis and PCP are experienced, more often than not, as euphoric. However, *anhedonia* seems to be one of the most chronic symptoms of schizophrenia, as it is suggested by the works of Loas [111].

In the end, the pharmacological models studied so far, although reliable, never reproduce more than a part of the complex schizophrenia phenomenology. As such, that observation goes hand in hand with the common view of schizophrenia as a pathology of general cerebral disconnectivity that would affect a plurality of neurotransmitter systems.

ACKNOWLEDGEMENTS

The authors would like to pay tribute to Dr Jean-Yves Roy, a pioneer psychiatrist in dual diagnosis in Quebec, who passed away after the completion of this article.

ES is holder of the Eli Lilly Chair of Schizophrenia from the University of Montreal.

REFERENCES

- [1] Young D, Scoville WB. Paranoid psychosis in narcolepsy and the possible danger of benzedrine treatment. *Med Clin North Amer* 1938; 22: 637-46.
- [2] Angrist BM, Gershon S. The phenomenology of experimentally induced amphetamine psychosis: preliminary observations. *Biol Psychiatry* 1970; 2: 95-107.
- [3] Griffith JD, Cavanaugh J, Oates J. Schizophreniform psychosis induced by large-dose administration of D-amphetamine. *J Psychedelic Drugs* 1969; 2: 42-8.
- [4] Ziedonis D, Steinberg ML, Smelson D, Wyatt S. Chapter 4: Co-occurring addictive and psychotic disorders. In: Graham AW, Schultz TK, Mayo-Smith NF, Ries RK & Wilford BB (eds.) *Principles of Addiction Medicine*. ASAM. 2003; 1297-1319.
- [5] Cutting J. A reappraisal of alcohol psychoses. *Psychol Med* 1978; 8: 285-305.
- [6] McKenna C. Substances-induced psychiatric disorders. In: Miller NS (ed.) *The Principles and Practice of Addictions in Psychiatry*. WB Saunders Company. 1997; 103-18.
- [7] Soyka M. Psychopathological characteristics in alcohol hallucinosis and paranoid schizophrenia. *Acta Psychiatr Scand* 1990; 81: 255-9.
- [8] Soyka M, Raith L, Steinberg R. Mean age, sex ratio and psychopathology in alcohol psychoses. *Psychopathology* 1988; 21: 19-25.
- [9] Bell DS. The experimental reproduction of amphetamine psychosis. *Arch Gen Psychiatry* 1973; 29: 35-40.
- [10] Bell DS. Comparison of amphetamine psychosis and schizophrenia. *Br J Psychiatry* 1965; 111: 701-7.
- [11] Grinspoon L, Hedblom P. Effects of short- and long-term use. In: *The Speed Culture*. Harvard University Press. 1975; 112-48.
- [12] Harris D, Batki SL. Stimulant psychosis: symptom profile and acute clinical course. *Am J Addictions* 2000; 9: 28-37.
- [13] Janowsky DS, Risch C. Amphetamine psychosis and psychotic symptoms. *Psychopharmacology* 1979; 65: 73-7.
- [14] Snyder SH. A "model schizophrenia" mediated by catecholamines. In: Smith DE (ed.) *Amphetamine use, Misuse and Abuse*. GK Hall & Co. 1979; 189-204.
- [15] Basu D, Malhotra A, Varma VK. Cannabis psychosis and acute schizophrenia. *Eur Addict Res* 1999; 5: 71-3.
- [16] Imade AGT, Ebie JC. A retrospective study of symptom patterns of cannabis-induced psychosis. *Acta Psychiatr Scand* 1991; 83: 134-6.
- [17] Nunez LA, Gurpegui M. Cannabis-induced psychosis: a cross-sectional comparison with acute schizophrenia. *Acta Psychiatr Scand* 2002; 105: 173-8.
- [18] Thacore VR. Cannabis psychosis and paranoid schizophrenia. *Arch Gen Psychiatry* 1976; 33: 383-6.
- [19] Allen MR, Young SJ. Phencyclidine-induced psychosis. *Am J Psychiatry* 1978; 135 (9): 1081-4.
- [20] Jacob MS, Carlen PL. Phencyclidine ingestion: drug abuse and psychosis. *Int J Addictions* 1981; 16 (4): 749-58.
- [21] Luisada PV. The phencyclidine psychosis: phenomenology and treatment. *NIDA Res Monogr Series* 1978; 21: 241-53.
- [22] Seeman P, Lee T, Chau-Wong M, Wong K. Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature* 1976; 261: 717-9.
- [23] Grace AA. Cortical regulation of subcortical dopamine systems and its possible relevance to schizophrenia. *J Neural Transmission* 1993; 91: 111-134.
- [24] Gardner EL. Brain reward mechanisms. In: Lowinson JH, et al. (eds.) *Substance Abuse: A Comprehensive Textbook* (3rd edition). Baltimore: Williams & Wilkins. 1997; 51-85.
- [25] Pierce CR, Kalivas PW. A circuitry model of the expression of behavioural sensitization to amphetamine-like psychostimulants. *Brain Res Rev* 1997; 192-216.
- [26] Lieberman JA, Kane JM, Alvir J. Provocative tests with psychostimulant drugs in schizophrenia. *Psychopharmacology* 1987; 91: 415-33.
- [27] Breier A, Su T-P, Saunders R, et al. Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine

- concentrations: evidence from a novel positron emission tomography method. *Proc Natl Acad Sci USA* 1997; 94: 2569-74.
- [28] Laruelle M, Abi-Dargham A. Dopamine as the wind of the psychotic fire: new evidence from brain imaging studies. *J Psychopharmacology* 1999; 13 (4): 358-71.
- [29] Mathew RJ, Wilson WH. Changes in cerebral blood flow and mental state after amphetamine challenge in schizophrenic patients. *Neuropsychobiology* 1989; 21: 117-23.
- [30] Abi-Dargham A. Recent evidence for dopamine abnormalities in schizophrenia. *Eur Psychiatry* 2002; 17 suppl 4: 341-7.
- [31] Glatt SJ, Faraone SV, Tsuang MT. Association between a functional catechol-O-methyltransferase gene polymorphism and schizophrenia: meta-analysis of case-control and family-based studies. *Am J Psychiatry* 2003a; 160 (3): 469-76.
- [32] Wise RA. The anhedonia hypothesis: mark III. *Behav Brain Sci* 1985; 8: 178-86.
- [33] Panksepp J. *Affective Neuroscience: The Foundations of Human and Animal Emotions*. Oxford: Oxford University Press. 1998.
- [34] Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Brain Res Rev* 1993; 18: 247-92.
- [35] Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology and pharmacology in schizophrenia. *Am J Psychiatry* 2003; 160: 13-23.
- [36] Regier DA, Farmer ME, Rae DS, *et al.* Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) Study. *JAMA* 1990; 264 (19): 2511-8.
- [37] Wise R, Rompré PP. Brain dopamine and reward. *Ann Rev Psychol* 1989; 40: 191-225.
- [38] Lipska BK, Kaskiw GE, Weinberger DR. Postpubertal emergence of hyperresponsiveness to stress and to amphetamine after neonatal excitotoxic hippocampal damage: a potential animal model of schizophrenia. *Neuropsychopharmacology* 1993; 9: 67-75.
- [39] Chambers AR, Self DW. Motivational responses to natural and drug rewards in rats with neonatal ventral hippocampal lesions: an animal model of dual diagnosis schizophrenia. *Neuropsychopharmacology* 2002; 27: 889-905.
- [40] Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry* 1996; 153 (3): 321-30.
- [41] Martucci L, Kennedy L. Dopamine genes and neuropsychiatric disease. In: Bolis CL, Pani L & Licinio J (eds.) *Dopaminergic System: Evolution from Biology to Clinical Aspects*. Philadelphia: Lippincott, Williams & Wilkins. 2001; 181-92.
- [42] Glatt SJ, Faraone SV, Tsuang MT. Meta-analysis identifies an association between dopamine D2 receptor gene and schizophrenia. *Mol Psychiatry* 2003; 8: 911-5.
- [43] Kane J, Hogfeld G, Singer J, Meltzer H, and the Clozaril Collaborative Study Group. Clozapine for the treatment-resistant schizophrenic. *Arch Gen Psychiatry* 1988; 45: 789-96.
- [44] Ashby CR, Wang RY. Pharmacological actions of the atypical antipsychotic drug clozapine: a review. *Synapse* 1996; 24: 349-94.
- [45] Corrigan MH, Gallen CC, Bonura ML, Merchant KM, Sonepiprazole Study Group. Effectiveness of the selective D4 antagonist sonepiprazole in schizophrenia: a placebo-controlled trial. *Biol Psychiatry* 2004; 55 (5): 445-51.
- [46] Stockings GT. A clinical study of the mescaline psychosis, with special reference to the mechanism of the genesis of schizophrenic and other psychotic states. *J Ment Science* 1940; 86: 29-47.
- [47] Hollister LE. Drug-induced psychoses and schizophrenic reactions: a critical comparison. *Ann New York Acad Sci* 1962; 96: 80-8.
- [48] Hays P, Tilley JR. The differences between LSD psychosis and schizophrenia. *Can Psychiatry Assoc J* 1973; 18: 331-3.
- [49] Vardy MM, Kay SR. LSD psychosis or LSD-induced schizophrenia? *Arch Gen Psychiatry* 1983; 40: 877-83.
- [50] Gouzoulis-Mayfrank E, Habermeyer E, Hermle L, Steinmeyer AM, Kunert HJ, Sass H. Hallucinogenic drug induced states resemble acute endogenous psychoses: results of an empirical study. *Eur Psychiatry* 1998; 13: 399-406.
- [51] Meltzer HY, Matsubara S, Lee J-C. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin 2 pKi values. *J Pharmacol Exp Ther* 1989; 251 (1): 238-46.
- [52] Lewis R, Kapur S, Jones C, *et al.* Serotonin 5-HT₂ receptors in schizophrenia: A PET study using (¹⁸F)setoperone in neuroleptic-naïve patients and normal subjects. *Am J Psychiatry* 1999; 156 (1): 72-8.
- [53] Kapur S, Remington G. Serotonin – dopamine interaction and its relevance to schizophrenia. *Am J Psychiatry* 1996; 153: 466-76.
- [54] Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. *Arch Gen Psychiatry* 2003; 60: 553-64.
- [55] Keefe RSE, Silva SG, Perkins DO, Lieberman JA. The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis. *Schizophr Bull* 1999; 25 (2): 201-22.
- [56] 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: 51-68.
- [57] Lahti AC, Holcomb HH, Weiler MA, Medoff DR, Tamminga CA. Functional effects of antipsychotic drugs: comparing clozapine with haloperidol. *Biol Psychiatry* 2003; 53 (7): 601-8.
- [58] Stip E, Fahim C, Mensour B, Leroux JM, Beaudoin G, Beaugard M. Does blunted in schizophrenia improve with quetiapine? a functional magnetic imaging preliminary results. In *J Neuropsychopharmacol* 2002; 5 (suppl 1): S72-3.
- [59] Meltzer HY, Arvanitis L, Bauer D, Rein W. Meta-Trial Study Group. Placebo-controlled evaluation of four novel compounds for the treatment of schizophrenia and schizoaffective disorder. *Am J Psychiatry* 2004; 161: 975-84.
- [60] Leucht S, Pitschel-Walz G, Engel RR, Kissling W. Amisulpride, an unusual "atypical" antipsychotic: a meta-analysis of randomized controlled trials. *Am J Psychiatry* 2002; 159: 180-90.
- [61] Zukin SR, Zukin RS. Specific (3H)phencyclidine binding in rat central nervous system. *Proc Natl Acad Sci USA* 1979; 76: 5372-6.
- [62] Adler CM, Malhotra AK, Elman I, *et al.* Comparison of ketamine-induced thought disorder in healthy volunteers and thought disorder in schizophrenia. *Am J Psychiatry* 1999; 156: 1646-9.
- [63] Krystal JH, Karper LP, Seibyl JP, *et al.* Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. *Arch Gen Psychiatry* 1994; 51: 199-214.
- [64] Lahti AC, Weiler MA, Michaelidts T, Parwani A, Tamminga CA. Effects of ketamine in normal and schizophrenic volunteers. *Neuropsychopharmacology* 2001; 25: 455-67.
- [65] Newcomer JW, Farber NB, Jevtic-Todorovic V, *et al.* Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. *Neuropsychopharmacology* 1998; 20: 106-18.
- [66] Abi-Saab WM, D'Souza CD, Moghaddam B, Krystal JH. The NMDA antagonist model for schizophrenia: promises and pitfalls. *Pharmacopsychiatry* 1998; 31 suppl.: 104-9.
- [67] Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry* 1991; 148 (10): 1301-8.
- [68] Miyamoto S, Stroup TS, Duncan GE, Aoba A, Lieberman JA. Chapter 24: Acute pharmacological treatment of schizophrenia. In: Hirsch SR, Weinberger D (eds.) *Schizophrenia* (2nd edition). Malden: Blackwell Science. 2003; 443-73.
- [69] Kapur S, Seeman P. NMDA receptor antagonists ketamine and PCP have direct effects on the dopamine D2 and serotonin 5-HT₂ receptors –implications for models of schizophrenia. *Mol Psychiatry* 2002; 7: 837-44.
- [70] Moghaddam B, Krystal JH. The neurochemistry of schizophrenia. In: Hirsch SR & Weinberger D (eds.) *Schizophrenia* (2nd edition). Malden: Blackwell Science. 2003; 349-64.
- [71] Moreau de Tours JJ. *Du Haschich et de l'Aliénation Mentale*. Paris : Masson; 1845.
- [72] Iversen LL. *The Science of Marijuana*. Oxford University Press. 2000.
- [73] Emrich HM, Leweke M, Schneider U. Towards a cannabinoid hypothesis of schizophrenia: cognitive impairments due to dysregulation of the endogenous cannabinoid system. *Pharma Biochem Behav* 1997; 56 (4): 803-7.
- [74] Mathew RJ, Wilson WH, Chiu NY, Turkington TG, Degrado TR, Coleman RE. Regional cerebral blood flow and depersonalization after tetrahydrocannabinol administration. *Acta Psychiatr Scand* 1999; 100: 67-75.

- [75] Ghodse HA. Cannabis psychosis. *Br J Addiction* 1986; 81: 473-8.
- [76] Thornicroft G, Meadows G, Politi P. Is "cannabis psychosis" a distinct category? *Eur Psychiatry* 1992; 7: 277-82.
- [77] Johns A. Psychiatric effects of cannabis. *Br J Psychiatry* 2001; 178: 116-22.
- [78] Verdoux H, Sorbara F, Gindre C, Swendsen JD, Van Os J. Cannabis use and dimensions of psychosis in a nonclinical population of female subjects. *Schizophr Res* 2002; 59: 77-84.
- [79] Williams JH, Wellman NA, Rawlins JN. Cannabis use correlates with schizotypy in healthy people. *Addiction* 1996; 91 (6): 869-77.
- [80] Linszen DH, Dingemans PM, Lenior ME. Cannabis abuse and the course of recent-onset schizophrenic disorders. *Arch Gen Psychiatry* 1994; 51: 273-9.
- [81] Andreasson S, Allebeck P, Engstrom A, Ryberg U. Cannabis and schizophrenia: a longitudinal study of Swedish conscripts. *Lancet* 1987; 2 (8574): 1483-6.
- [82] Hall W, Degenhardt L. Cannabis use and psychosis: a review of clinical and epidemiological evidence. *Austr Nz J Psychiatr* 2000; 34: 26-34.
- [83] Van Os J, Bak M, Hanssen M, Bijl RV, de Graaf R, Verdoux H. Cannabis use and psychosis: A longitudinal population-based study. *Am J Epidemiology* 2002; 156 (4): 319-27.
- [84] Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. Cannabis use in adolescence and risk for adult psychosis: Longitudinal prospective study. *Brit Med J* 2002; 325: 1212-3.
- [85] Ferguson DM, Horwood LJ, Swain-Campbell NR. Cannabis dependence and psychotic symptoms in young people. *Psychol Med* 2003; 33: 15-21.
- [86] Tien AY, Anthony JC. Epidemiological analysis of alcohol and drug use as risk factors for psychotic experiences. *J Nerv Ment Dis* 1990; 178 (8): 473-80.
- [87] Degenhardt L, Hall W, Lynskey M. Testing hypotheses about the relationship between cannabis use and psychosis. *Drug Alcohol Depend* 2003; 71: 37-48.
- [88] Phillips LJ, Curry C, Yung AR, Yuen HP, Adlard S, McGorry PD. Cannabis use is not associated with the development of psychosis in an "ultra" high risk group. *Austr NZ J Psychiatry* 2002; 36: 800-6.
- [89] Allebeck P, Adamsson C, Engström A, Rydberg U. Cannabis and schizophrenia: A longitudinal study of cases treated in Stockholm County. *Acta Psychiatr Scand* 1993; 88: 21-4.
- [90] Andreasson S, Allebeck P, Rydberg U. Schizophrenia in users and nonusers of cannabis: A longitudinal study in Stockholm County. *Acta Psychiatr Scand* 1989; 79: 505-10.
- [91] Kwapił TR. A longitudinal study of drug and alcohol use by psychosis-prone and impulsive-nonconforming individuals. *J Abnormal Psychol* 1996; 105 (1): 114-23.
- [92] 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. *Brit Med J* 2002; 325: 1199-1203.
- [93] Solowij N, Michie PT, Fox AM. Effects of long-term cannabis use on selective attention: an event-related potential study. *Pharma Biochem Behav* 1991; 40: 683-8.
- [94] Ameri A. The effects of cannabinoids on the brain. *Progr Neurobiol* 1999; 58: 315-38.
- [95] Leweke FM, Giuffrida A, Wurster U, Emrich HM, Piomelli D. Elevated endogenous cannabinoids in schizophrenia. *NeuroReport* 1999; 10: 1665-9.
- [96] Dean B, Sundram S, Bradbury R, Scarr E, Copolov D. Studies on (³H)CP-55940 binding in the human central nervous system: regional specific changes in density of cannabinoid-1 receptors associated with schizophrenia and cannabis use. *Neuroscience* 2001; 103 (1): 9-25.
- [97] Leroy S, Griffon N, Bourdel MC, Olié JP, Poirier MF, Krebs MO. Schizophrenia and the cannabinoid receptor type 1 (CB1): association study using a single-base polymorphism in coding exon 1. *Am J Med Gen* 2001; 105: 749-52.
- [98] D'Souza CD, Belger A, Abi-Saab W, Adams S, Gil R, Larvey K, *et al.* Dose-response of THC effects in schizophrenics and healthy controls. *Biol Psychiatry* 1998; 43: 130S-131S.
- [99] Mechoulam R, Parker LA, Gallily R. Cannabidiol: an overview of pharmacological aspects. *J Clin Pharmacol* 2002; 42 (suppl. 11): S11-19.
- [100] Ben Amar M, Champagne P, Vallée R, Cyr J-F, Léonard L, Charbonneau J. Alcohol. In: *Les Psychotropes: Pharmacologie et toxicomanie*. Montréal: Presses de l'Université de Montréal. 2002; 221-303.
- [101] Hunglund BL, Basavarajappa BS. Are anandamide and cannabinoid receptors involved in ethanol tolerance? a review of the evidence. *Alcohol Alcohol* 2000; 35 (2): 126-33.
- [102] Soyka M, Dresel S, Horak M, Ruther T, Tatsch K. PET and SPECT findings in alcohol hallucinosis: case report and super-brief review of the pathophysiology of this syndrome. *World J Biol Psychiatry* 2000; 1 (4): 215-8.
- [103] Soyka M, Zetzsche T, Dresel S, Tatsch K. FDG-PET and IBZM-SPECT suggest reduced thalamic activity but no dopaminergic dysfunction in chronic alcohol hallucinosis. *J Neuropsychiatry Clin Neurosci* 2000; 12 (2): 287-8.
- [104] Perry EK, Perry RH. Acetylcholine and hallucinations: disease-related compounds to drug-induced alterations in human consciousness. *Brain Cogn* 1995; 28: 240-58.
- [105] McBride T, Moberg PJ, Arnold SE, *et al.* Neuropsychological functioning in elderly patients with schizophrenia and Alzheimer's disease. *Schizophr Res* 2002; 55 (3): 217-27.
- [106] Bymaster FP. Possible role of muscarinic receptor agonists as therapeutic agents for psychosis. In: Breier A "and others" (eds.) *Current Issues in the Psychopharmacology of Schizophrenia*. Philadelphia: Lippincott, Williams & Wilkins. 2001; 333-48.
- [107] Bymaster FP, Felder CC, Tzavara E, Nomikos GG, Calligaro DO, Mckinzie DL. Muscarinic mechanisms of antipsychotic atypicality. *Progr Neuro-Psychopharmacol Biol Psychiatry* 2003; 27: 1125-43.
- [108] Dalack GW, Healy DJ, Meador-Woodruff JH. Nicotine dependence in schizophrenia: clinical phenomena and laboratory findings. *Am J Psychiatry* 1998; 155: 1490-1501.
- [109] Adler LE, Olincy A, Waldo M, *et al.* Schizophrenia, sensory gating and nicotinic receptors. *Schizophr Bull* 1998; 24 (2): 189-202.
- [110] Leonard S, Adams C, Breese CR, *et al.* Nicotinic receptor function in schizophrenia. *Schizophr Bull* 1996; 22 (3): 431-45.
- [111] Loas G, Noisette C, Legrand A, Boyer P, Delahousse J. Clinical characteristics of chronic schizophrenic patients presenting with severe anhedonia. *Encéphale* 1996; 22 (5): 351-8.