



# Cognitive changes in patients with acute phase psychosis—Effects of illicit drug use



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## ARTICLE INFO

### Article history:

Received 12 August 2013

Received in revised form

27 August 2014

Accepted 28 August 2014

Available online 8 September 2014

### Keywords:

Psychotic disorders

Cognition

Neuropsychology

Substance abuse

Schizophrenia

## ABSTRACT

Illicit drug use may influence cognition in non-affective psychosis. Previous studies have shown better cognition in psychosis with illicit drug use as compared to psychosis only. Possibly, illicit drug using patients have more transient drug-related cognitive deficits. Thus, the aim of the present study was to examine cognitive change the first weeks after admission to a psychiatric emergency ward, expecting more cognitive improvement at follow-up in the illicit drug group as compared to psychosis only. Patients with acute non-affective psychosis with (26%) and without illicit drug use were examined at baseline ( $n=123$ ) and follow-up ( $n=67$ ), with alternative forms of the Repeatable Battery for the Assessment of Neuropsychological Status. Latent Growth Curve models, controlling for cognition at baseline and age differences between the groups, were used to analyze cognitive change. The illicit drug using patients showed the largest improvement in cognition, especially among the youngest patients. Younger patients with non-affective psychosis and illicit drug use showed more cognitive improvement the first weeks after acute psychosis as compared to psychosis only. This suggests that the illicit drug users constitute a sub-group with less stable cognitive deficits and less cognitive vulnerability.

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## 1. Introduction

Extensive use of illicit drugs is common in patients with non-affective psychosis, typically about 40–50% of patients with psychosis report lifetime substance use disorder (Regier et al., 1990; Kovasznay et al., 1997; Blanchard et al., 2000; Margolese et al., 2004). The range of reported substance use disorder is large in psychosis, however, from 10% to 70%, depending on methodological differences and population characteristics (Jimenez-Castro et al., 2011). Rates of cannabis use have been found to be especially high; a review reported that median rate for current cannabis use disorder was 28.6% in first-episode and 22.0% for more long-lasting non-affective psychosis (Koskinen et al., 2010). Substance use in psychosis has been associated with more hospitalizations, non-adherence, heightened suicide risk and adverse long-term clinical outcomes compared to patients with psychosis who do not use illicit drugs (Talamo et al., 2006; Zammit et al., 2008; Schmidt et al., 2011; Large et al., 2014; Sara et al., 2014; Tarricone et al.,

2014). Some of the most frequently used illicit drugs, cannabis and stimulants (Ringén et al., 2008; Helseth et al., 2009; Koskinen et al., 2010), may induce transient positive psychosis symptoms and cognitive alterations (Curran et al., 2004; D'Souza et al., 2005, 2009; Smith et al., 2009).

A majority of patients with schizophrenia and non-affective psychoses have clinical significant cognitive deficits (Keefe and Fenton, 2007; Palmer et al., 2009; Lewandowski et al., 2011), often depicted as a vulnerability factor that is present also before the development of psychosis (Woodberry et al., 2008) and in high-risk populations (Brewer et al., 2005; Woodberry et al., 2010). It is likely, however, that the use of illicit drugs influences cognition in psychosis. Experimental studies have shown that the most prominent psychoactive substance in cannabis, Delta-9-tetrahydrocannabinol (THC), have an especially strong negative effect on cognition in individuals with psychosis (D'Souza et al., 2005; Henquet et al., 2006). Most studies, have found better cognitive functioning in psychosis patients with lifetime or previous illicit drug use as compared to psychosis alone (Potvin et al., 2008; Løberg and Hugdahl, 2009; Rabin et al., 2011; Yucel et al., 2012), although this has not been consistently shown in all studies (e.g. Wobrock et al., 2013). Furthermore, for cannabis, superior cognitive functioning in

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the illicit drug using group has been reported in first episode psychosis patients (Rodriguez-Sanchez et al., 2010; Cunha et al., 2013) and at 10-year follow-up after onset of psychosis (Stirling et al., 2005), and replicated by means of functional Magnetic Resonance Imaging (fMRI) (Løberg et al., 2012). Whilst intake of THC has been associated with transient cognitive deficits (D'Souza et al., 2005, 2009), mixed results for the intake of stimulants have been reported with both better (Barch and Carter, 2005; Bahorik et al., 2013) and worse (Meijer et al., 2012) cognitive performance in non-affective psychosis. It is likely that the effect of both cannabis and stimulants use on cognition in patients with non-affective psychosis is time-related (Løberg and Hugdahl, 2009). Possibly, current illicit drug use, like cannabis, influence cognition more negatively, while previous drug use is a marker of a different pathway to psychosis. The illicit drug using psychotic patients may constitute a sub-group with less cognitive vulnerability (Løberg et al., 2012; Ferraro et al., 2013); illicit drug use may have a more temporary influence on cognition, generating a short-term cognitive and psychotic breakdown (Løberg and Hugdahl, 2009). Thus, illicit drug use, like cannabis, may create transient deficits in cognition paralleling the period of acute psychosis.

To test this hypothesis, it is necessary to examine the change of cognitive functioning from the time of an acute psychotic breakthrough to the stabilization of psychotic symptoms in patients with and without drug use. Furthermore, the drug using group should be abstinent from illicit drugs in the follow-up period to enable possible cognitive improvement. To accomplish this, only patients with symptoms of acute psychosis admitted to a psychiatric in-patient emergency department were included, and the patients were followed while hospitalized to minimize use of illicit drugs. By 4–6 weeks most of the long-term effects of illicit drug use should be minimized, and most psychosis symptoms responding to treatment (Sherwood et al., 2006; Szoke et al., 2008). Follow-up was therefore set to time of discharge from the acute ward or after 6 weeks at the latest, if not discharged earlier. This was allowed for both a naturalistic prognostic design and a reduction of variability in regard to time to follow-up. Furthermore, a brief neuropsychological screening instrument with alternative forms; the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), was used to minimize potential practice effects (Randolph, 1998; Gold et al., 1999; Beglinger et al., 2005). Earlier longitudinal studies on cognitive functioning have usually not addressed the issue of practice effects sufficiently (Goldberg et al., 2007, 2010). Practice effects can be particularly evident when there are short time intervals between repeated neuropsychological testing, and the effect seems to be strongest from baseline to the second testing (Hausknecht et al., 2007; Bartels et al., 2010). Latent Growth Curve modeling was chosen to examine cognitive trajectories from baseline to follow-up in order to minimize the effect of missing data, controlling for the baseline level in cognitive functioning and varying test–retest intervals.

The aim of the present study was to compare cognitive changes in non-affective psychosis patients with illicit drug use to cognitive changes in non-affective psychosis patients with no illicit drug use after an acute psychotic episode. It was hypothesized that the drug group would show more improvement in cognitive functioning from time of admission to a psychiatric emergency ward to time of discharge from the acute ward or after 6 weeks at the latest.

## 2. Methods

### 2.1. Study design

All patients were recruited from an acute psychiatric emergency ward at Haukeland University Hospital, Bergen, Norway, through an extensive clinical research project; the Bergen Psychosis Project (BPP). This project was a 24-month,

prospective, rater-blind, pragmatic, randomized, head-to-head comparison of the effectiveness of risperidone, olanzapine, quetiapine, and ziprasidone (see Johnsen et al. (2010), for details). Thus, all patients were candidates for oral antipsychotic drug therapy. The present study used data from the period the patients were in-patients at the psychiatric emergency ward. Baseline was defined as the time of admittance to the ward, and follow-up was defined as time of discharge from the acute ward or after 6 weeks at the latest, if not discharged earlier, except for three patients that for practical reasons were followed-up between 7 and 11 weeks. The mean time period from baseline to follow-up was 4 weeks ( $M=4.03$ ,  $S.D.=2.13$ ,  $Mdn=3.71$ ). The first inclusion of patients to the present study took place the 9th of March 2004 and the last patient was included the 13th of January 2009. The project was approved by the Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services. The Regional Committee for Medical Research Ethics allowed eligible patients to be included before informed consent was provided, thus entailing a clinically relevant representation in the study.

### 2.2. Subjects

#### 2.2.1. Inclusion criteria and sample characteristics

Criteria for inclusion were symptoms of active non-affective psychosis, determined by a score of four or over on one or more of the items Delusions, Hallucinatory behavior, Grandiosity, Suspiciousness/Persecution, or Unusual thought content from the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1989). Patients with affective psychoses and drug-induced psychosis were excluded, and all patients met the ICD-10 diagnostic criteria (WHO, 2004) for schizophrenia, schizoaffective disorder, acute and transient psychotic disorder, delusional disorder and non-organic psychotic disorder. The diagnoses were determined by psychiatrists or specialists in clinical psychology. Patients were excluded if they were not able to understand Norwegian, had a history of head injury or mental retardation. In addition, patients under the influence of illicit drugs during testing were excluded. There were 123 patients at baseline and 67 patients at follow-up. Demographic, clinical and cognitive characteristics by group and time of assessment are provided in Table 1.

#### 2.2.2. Drug groups

Information on illicit drug use was based on the Clinician Drug Use Scale (CDUS) and alcohol use was based on the Clinician Alcohol Use Scale (CAUS) (Drake et al., 1990). The scales have similar structures. The drug use scale rates clinically significant illicit drug use in severe mental illness on a scale from 1 to 5 ranging from abstinence (1), use without impairment (2), abuse (3), dependent (4), and severe dependence (5) the last 6 months (Drake et al., 1996). The patients' drug use in the present study was rated by a trained psychiatrist, and the threshold was set at "use without impairment". The psychiatrist used all available information over the 6 last months when evaluating the illicit drug use. The Clinician Drug Use scale has shown excellent reliability and increase of validity when multiple sources are used for rating severity of drug use, in addition to high sensitivity and specificity (Drake et al., 1990). Patients were split into two groups at baseline according to the presence of drug use. A psychosis group without drug use ( $n=91$ ), and a group with both psychosis and concurrent drug use ( $n=32$ ). To further decrease false negative drug users all the patients' clinical records were carefully examined by a trained psychiatric research nurse for use of cannabis as a marker of drug use, as it is possible that cannabis use could be underreported (Bahorik et al., 2014). All 32 patients in the psychosis group with drug use had a lifetime history of cannabis use. In addition, the distribution of additional drug use as reported by use of Drug Use Scale was the following: stimulants;  $n=6$ , stimulants, sedatives, hypnotic, anxiolytic;  $n=3$ , opiates and stimulants;  $n=2$ , stimulants, sedatives, hypnotic, anxiolytic, opiates;  $n=1$ . There were 72 urine tests administered at baseline, seven of these patients tested positive on cannabis, two on amphetamines and one on opiates, 33 on benzodiazepines. As part of the admission to the psychiatric emergency ward, hospital staff examines the patients' property in search for substances. Urine tests are administered if an in-patient appears intoxicated or is suspected to have been using illicit drugs. In the psychosis groups with and without illicit drug use the distribution of the ICD-10 primary psychosis diagnosis was the following at baseline: schizophrenia spectrum; 62.5%, 39.5%, acute and transient psychotic disorders; 34.4%, 49.5%, and non-organic psychotic disorders; 3.1%, 11.0%, respectively. At 1 month follow-up the distribution of psychosis diagnosis was similar to baseline distribution in the psychosis groups without and with illicit drug use: schizophrenia spectrum; 62.6%, 38.5%, acute and transient psychotic disorders; 31.2%, 51.9%, non-organic psychotic disorder; 6.2%, 9.6%.

### 2.3. Assessments

#### 2.3.1. Cognitive assessments

To assess cognitive impairments the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph, 1998) was administered at baseline and follow-up to assess cognitive impairments in patients with psychosis by trained psychiatric research nurses. RBANS is a cognitive screening instrument that can be used to examine cognitive change when administered successively

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