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A Secondary Analysis from a Randomised Controlled Trial

Substance Use Disorder and Delusional Symptoms in Patients with Psychosis

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Background

Co-occurring substance use disorders (SUD) with severe mental illness are very common and have an important impact on treatment and outcomes. Patients with psychotic disorders are much more likely to suffer from SUD than the general population [1], with rates for lifetime SUD and psychotic disorder ranging from 20-60% [2, 3]. Concurrent SUD is more often associated with male gender, younger age, single marital status [4-6], conduct disorder and antisocial personality disorder [7, 8]. Even higher rates of SUD were reported amongst first episode psychosis patients [9-11]. Alcohol and cannabis are substances commonly consumed by dual diagnosed patients [12, 13], but the substances used with psychosis vary among patients [14]. Consuming multiple substances is common. Weaver et al. [13] found that 40% of patients with problematic drug use were also misusing alcohol. The consequences of SUD for patients with psychosis have been widely demonstrated. Substance use is linked to a more severe psychopathology [15, 16] with a higher positive [17–19] and negative symptom level [17, 20], greater interpersonal and family problems, as well as less self-efficacy [6] and a more severe course of the illness with a higher mortality rate [21]. Patients with dual diagnosis have been found to show lower rates of treatment compliance [22, 23]. Psychosocial

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instability, lower motivation levels and higher symptom levels, as well as higher perception of stigma, especially in patients with first-episode psychosis [24], may be barriers to accessing treatment. Patients with co-occurring disorders also find it more difficult to engage in traditional treatment plans [25]. A lack of services treating patients with dual diagnosis can, in part, explain the worse treatment outcomes. An assessment of services across the United States found that only 18% of addiction and 9% of mental health programs were offering integrated treatment [26]. While the importance of treating patients with psychosis and co-morbid SUD is clear, there is still need for the development of treatments and studies related to these concerns to improve the evidence in this domain [27]. However, some preliminary studies have found patients with mental disorders and co-occurring SUD to achieve clinical improvement similar to patients without SUD [28, 29]. Among others, cognitive behaviour therapy has been found effective as a conjunct treatment for psychosis [30–32].

Although some studies show lower overall functional outcomes linked to persisting SUD outcomes [16, 20], research on the impact of SUD on cognitive functioning and delusional thinking shows varying results [19, 33]. As mentioned above, more positive symptoms including delusions and hallucinations have been linked to SUD in first episode psychosis [18, 34, 35]. Delusional thinking impacts information processing and is often resistant to change despite treatment, making it an important measurement for treatment outcome [36-38]. The multidimensional concept of delusional beliefs can be divided into three components: distress, preoccupation and conviction of delusions [39]. These can be measured using Peters et al. Delusions Inventory (PDI-21) [40]. To our knowledge, no studies have specifically examined the impact of SUD on delusional thinking measured with the PDI-21.

In our analysis we would like to measure the impact of SUD on delusional thinking measured with the PDI-21 subscales. There is little literature examining the impact of SUD on these specific treatment outcomes compared to patients without SUD in programs for psychosis. As SUD has often been shown to negatively impact delusional thinking and to be linked to higher positive symptom levels in patients with psychosis, we hypothesised that there would be a difference in change over time for delusional thinking between SUD and No SUD participants.

Abstract

Background: Delusional thinking and low belief flexibility are important treatment targets in patients with psychotic disorders. Game-based interventions may improve hypothetical reasoning. As co-occurring substance use disorders (SUD) and psychotic disorders are common, the current study explores whether SUD may have an impact on the change of delusional beliefs in patients with psychosis.

Methods: This study is a secondary analysis of a longitudinal, assessor blinded, randomised controlled trial, in which 172 patients with positive psychosis symptoms were randomised into an intervention targeting belief flexibility. An improvement over time was found in the Peters et al. Delusion Inventory sub-scales and the Brief Psychiatric Rating Scale outcomes in the treatment group. The current study explores whether co-occurring SUD may have an impact on this change. We used a one-way repeated measures analysis of variance (ANOVA) with SUD present (yes vs no) as the between-subject factor and time as the within-subject factor. As 29% of the patients were not investigated for SUD, we also performed a sensitivity analysis in which we examined the undiagnosed participants as a fully-fledged group, allowing the analysis of all 172 participants.

Results: There was no significant effect of SUD. However, an overall significant time effect was observed for distress ($F = 18.7$, $p < 0.001$), conviction ($F = 19.8$. $p < 0.001$), preoccupation ($F = 15.4$, $p < 0.001$) and BPRS ($F = 6.3$, $p = 0.002$). This means that all patients improved similarly on their reduction of all dimensions regardless of presenting an active SUD or not. The same analysis with a third group labelled "undiagnosed" almost replicated the above results.

Conclusions: The presence of concomitant SUD at baseline does not seem to influence treatment outcomes over time concerning delusional beliefs. Therefore, specialised programs for psychotic disorders can be as effective for patients with concurrent SUD as for patients with psychosis only.

Keywords: Psychosis; substance use disorders; delusional beliefs; peters delusion inventory; cognitive behaviour therapy; serious games

Methods

The current study is part of a multicentre longitudinal randomised controlled trial (RCT) which explored the effectiveness of a cognitive restructuring intervention in 172 patients with psychotic disorders. Full detail of the RCT is given elsewhere [41]. Nevertheless, a short summary is outlined in the following paragraph to provide context.

The patients were recruited from psychiatric outpatient centres in Switzerland, France, Monaco and Italy. Inclusion criteria were: having a psychotic disorder according to DSM-IV, aged 18–65 years and persistent positive psychotic symptoms at inclusion. The exclusion criteria were: organic brain disease, mental retardation, prior participation in the game group, cognitive therapy of psychotic symptoms at inclusion and important disorganisation.

In the original study, half of the participants were randomly assigned to a novel cognitive game-based intervention targeting belief flexibility and the other half to a standard treatment. The intervention consisted of a collaborative group game with 1-hour weekly sessions. It used 80 cards presenting different situations to train ability to reason with hypotheses. Pharmacological treatment for psychosis and psychosocial care were offered to all of them. Primary and secondary outcomes were measured before the intervention (T1), three months after the intervention (T2) and again six months later (T3) in a repeated ANOVA design. The conviction subscale of the PDI-21, taken as the main outcome measure, showed an improvement in delusional thinking over time in the intervention group. The protocol of the original study was approved by institutional review boards and the Ethics Committees in Switzerland (Geneva), France and Italy. It is registered under the reference ISRCTN37178153.

Given that the possible effect of SUD was not assessed in the main study, the current report filled this gap by investigating in secondary analysis [35] whether this comorbidity might have an impact on the above-cited findings. Therefore, we conducted a repeated one-way between-groups ANOVA to explore the effect of SUD on PDI-21 subscale scores and Brief Psychiatric Rating Scale total score [42]. The Mini International Neuropsychiatric Interview [43] served to identify patients with SUD.

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Measures

Mini International Neuropsychiatric Interview (MINI) [43]

The MINI, a standardised interview, was developed to identify psychiatric disorders according to the DSM-IV. The validated French form was used [44]. The MINI, which was validated within the general population, has good validity, reliability, sensitivity and specificity indices [44, 45]. Patients were investigated with the MINI questionnaire for their actual alcohol use and other illegal substances, ending up with an abuse or dependence diagnosis. Following the assessment, of the initial 172 participants, 122 were formally diagnosed with or without SUD and 50 could not be diagnosed for lack of information, leaving a sample of 122 with complete data for analysis. Of these, seven patients presented alcohol abuse and four a dependency. Nine patients presented abuse of another psychoactive substance and ten a dependency. Due to the small number of patients presenting a SUD, we regrouped patients with abuse and dependency.

In total, 14.8% (N=18) were diagnosed as having a SUD in the same year while 85.2% (N=104) did not present a concomitant SUD.

Peters et al. Delusions Inventory (PDI) [39, 40]

The PDI was developed for use in the general population [39]. It consists of three dimensions (distress, preoccupation and conviction). A five-point Likert scale is used to measure 21 stated beliefs [40]. This questionnaire has shown good internal consistency, test-retest agreement and good concurrent validity pertaining to delusional ideation [46], magical ideation [47] and schizotypal measures [48]. Patients with psychotic disorders were found to have higher ratings on these scales compared to controls [39]. We used the French validated form of the scale [49].

Brief Psychiatric Rating Scale (BPRS) [42]

The BPRS measures psychiatric symptom levels. It uses a seven-point Likert scale from zero (not present) to six (extremely present) to measure 18 symptom constructs. The BPRS has shown good reliability and validity [50].

Statistical Analyses

Preliminary descriptive statistics, such as mean and standard deviation (SD) or percentages, were reported for demographic and clinical characteristics. Group comparisons were made using t-tests for continuous variables (or Mann-Whitney U test when required) and chi-square tests of homogeneity for categorical variables. To analyse the evolution of PDI subscores and BPRS total scores, we used a one-way repeated measures ANOVA first on a complete-case analysis basis with SUD membership (yes vs no) as the between-subject factor and time as the within-subject factor. Second, as missingness represents a non-negligible part of the study sample (29%), we performed a sensitivity analysis in which we analysed the undiagnosed participants as a fully-fledged group allowing the analysis of all 172 participants. The SUD variable then takes three categories: yes vs no vs undiagnosed. One-way repeated ANOVA design allows to separate out the effects of group and time and, more importantly, allows to analyse group-by-time interaction effects. To adjust for multiple testing with four outcomes measures considered, statistical significance was set at $p \leq 0.0125$. The statistical analyses were performed with SPSS software [51].

Results

The mean age of participants in the sample was around 37 years (SD=10.8). 22% of participants had attained a high school diploma or a university degree. The majority of the participants had a diagnosis of schizophrenia (84.4%), were single (80.3%) and more than half lived in a private residence (58.2%).

Except for age and living conditions, there were no statistical differences in the socio-demographic measures between patients with and without SUD. Patients with SUD were younger and more likely lived in residential places than those without SUD (p=0.03 and p=0.04 respectively). There was no other significant difference between the groups at baseline. See table 1 for further demographic and clinical characteristics.

Gender				0.3
• Male	60.6	72.2	62.3	
• Female	39.4	27.8	37.7	
Marital status				0.2
• Single	77.9	94.4	80.3	
• Other	22.1	5.6	19.7	
Highest educational degree obtained				0.5
• Primary/grammar school	53.9	61.1	55.0	
• Apprenticeship/professional school	22.5	27.8	23.3	
• High school/university	23.5	11.1	21.7	
Living conditions				0.04
• Private	62.5	33.3	58.2	
• Residential/other	37.5	66.7	41.8	
Diagnostic				1.0
• Schizophrenia	84.6	83.3	84.4	
• Other	15.4	16.7	15.6	
Benzodiazepines				0.4
• Yes	35.0	44.4	36.4	
• No	65.0	55.6	63.6	
PDI				
• Distress	22.1 (16.9)	26.2 (15.3)	22.7 (16.7)	0.3
• Conviction	28.4 (19.2)	30.9 (17.0)	28.8 (18.8)	0.6
• Preoccupation	21.9 (15.9)	24.7 (11.4)	22.3 (15.3)	0.5

Results of the repeated ANOVA showed no significant SUD effect on PDI distress, neither significant group-by-time interaction effect. However, an overall significant time effect was observed (F=18.7, p<0.001), meaning that a change over time in this outcome occurred for the total sample, independently of group membership. The tests of within-subjects contrasts showed that there were significant differences between T1 and T2 (p=0.01) and between T2 and T3 (p<0.001) (see table 2 and fig. 1).

…es over time for each group and for the whole sa

T1			T2	
SUD	All	No SUD	SUD	All
26.2 (15.3)	22.7 (16.7)	19.2 (15.3)	22.0 (11.2)	19.6 (
30.9 (17.0)	28.8 (18.8)	23.3 (17.4)	26.5 (10.6)	23.8 (
24.7 (11.4)	22.3 (15.3)	18.9 (14.5)	22.4 (10.8)	19.5 (
40.3 (7.1)	43.0 (10.4)	39.3 (10.5)	38.5 (9.6)	39.2 (

…entory, BPRS: Brief Psychiatric Rating Scale.

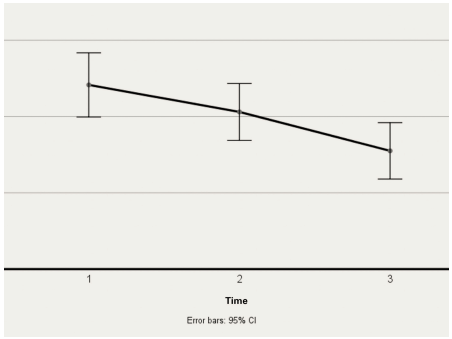

Figure 1: Evolution ot PDI Distress over time. PDI: Peters et al. Delusions Inventory; CI: Confidence interval.

Similarly, an overall significant time effect was observed for PDI conviction (F=19.8, p<0.001) but no group effect. The test of within-subjects contrasts showed significant differences between T1 and T2 (p=0.002) and T2 and T3 (p<0.001) (see table 2 and fig. 2).

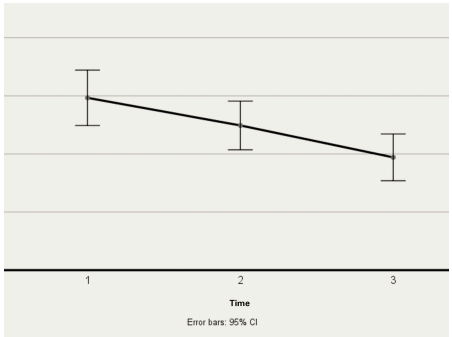

Figure 2: Evolution of PDI Conviction over time. PDI: Peters et al. Delusions Inventory; CI: Confidence interval.

The evolution of PDI preoccupation scores followed the same pattern as that observed for distress and conviction with one minor variation: the difference was not significant between T1 and T2 (p=0.05) taking account of the Bonferroni correction for multiple testing. As for the evolution between T2 and T3 the difference was highly significant (p<0.001) (see table 2 and fig. 3).

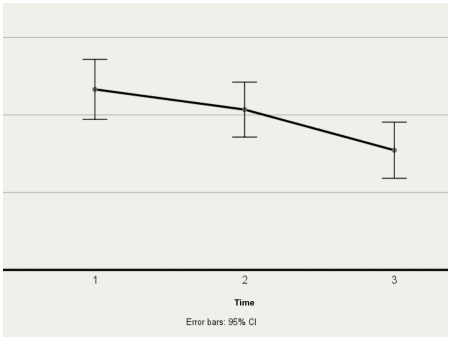

Figure 3: Evolution of PDI Preoccupation over time. PDI: Peters et al. Delusions Inventory; CI: Confidence interval.

As for BPRS, a significant overall time effect was observed (F=6.3, p=0.002). The test of within-subjects contrasts showed that this significant difference laid between T1 and T2 only (F=8.0, p=0.006). No other effect was detected (see table 2 and fig. 4).

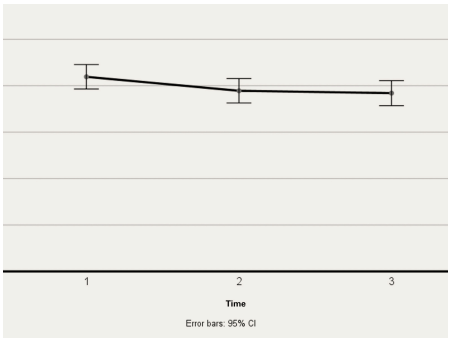

Figure 4: Evolution of BPRS over time. BPRS: Brief Psychiatric Rating Scale; CI: Confidence interval.

The same analyses were repeated with the missing participants as a 3rd "undiagnosed" group (detailed results not shown). There was an improvement over the complete case analysis results for the PDI subscales where all time effects were significant, including preoccupation, now being significant between T1 and T2 (p=0.002). The results for BPRS remained unchanged compared to the complete case analysis.

Discussion

The PDI distress, conviction and preoccupation subscores decreased over time. However, when analysing the interaction effect of group by time, the result was not statistically significant. This contradicts our hypothesis that SUD would influence the change over time in the PDI scores, implying that all patients improved similarly concerning a reduction in the three dimensions of delusional beliefs, regardless of presenting an active SUD or not. Lack of power might explain the finding as there were only a few patients with SUD in the sample. Another reason might also be that the usual pharmacological and psychosocial treatment received by all patients was equally effective, whether diagnosed with SUD or not.

The overall time effect observed in psychiatric symptom levels according to the BPRS was captured between T1 and T2 only. Nevertheless, these improvements regardless of SUD are important findings as this shows that specialised interventions are effective, despite SUD. It is interesting to note that this study sample of patients with SUD did not have a higher symptom level than patients without SUD (see table 1). This is interesting, as in literature SUD is often shown to be linked to higher symptom levels [17, 19]. However, the fact that the patients presenting SUD were twice as often housed in residential accommodations and on average younger, implies an overall lower psychosocial functioning, in concordance with other observations [52].

Other studies have found persistent substance use in patients with psychosis and concurrent SUD to be linked to less improvement on general outcome measures, such as functional outcomes, higher illness severity, more positive symptoms, higher service use, non-compliance, treatment drop-out and poor remission rates [2, 18, 20, 52, 53]. Low social functioning, financial problems and younger age in patients with schizophrenia have also been linked to treatment drop-out [54].

It is possible, that the more intensive treatment in the game-format group sessions may have improved their outcomes despite the SUD. The use of serious games has also been shown to improve treatment drop-out, which is generally higher in patients with co-occurring SUD [53, 55]. Such observations on social outcomes stress the needs to offer other comprehensive treatments targeting the social inclusion needs in addition to specific treatments, like the ones focusing on hypothetical hypothesis training [56, 57].

Certain studies specifically focused on integrating SUD treatment into their programs and measured the outcomes relative to substance use. Barrowclough et al. applied motivational interviewing, which was used as a complement to the usual treatment in their RCT [58]. Another RCT in a hospital setting integrated a SUD-specific group therapy to standard treatment [59]. Both studies found increased abstinence motivation and reduced substance use. The Canadian Schizophrenia Guidelines [60] and the NICE guidelines [61] recommend combined use of antipsychotic medication and psychosocial interventions for addictions. This has been confirmed by several studies which have suggested integrated treatment using antipsychotic medication as well as psychosocial interventions, cognitive behavioural therapy (CBT) and motivational interviewing for patients with dual diagnosis [58, 59]. Overall evidence suggests offering integrated motivational treatment with low threshold entry levels to improve treatment access for this vulnerable group of patients. Furthermore, studies examining treatments focusing on specific psychiatric symptoms have found these equally effective in improving psychiatric outcomes and can improve treatment engagement in individuals with and without SUD [22, 62]. Patients presenting concurrent SUD are sometimes treated in addiction programs rather than specialised psychiatric services for psychosis. Our findings imply, that these patients can equally benefit from treatment programs for psychosis. As a result, screening patients for co-occurring disorders is important in all psychiatric and addiction settings. Treatment programs for psychosis should be systematically offered to patients with co-occurring SUD, as they may improve long-term outcomes and functioning [28]. Equally, patients with coexisting disorders may also benefit from addiction programs. It is necessary to offer specific treatment options for both disorders as well as further develop specialised integrated programs. Unspecific factors, such as therapeutic alliance, are certain to play a role. Patients with SUD might specifically benefit from the attention given to them in intensive treatment programs. This could have influenced outcome measures. Studies have shown that substance use reduced up to 50% when patients were in treatment programs for psychosis [2, 20].

The group treatment offered to the participants of the study consisted of a serious game using CBT tools to improve patients' ability to find alternative hypothesis for different situations [41]. The game was well accepted by

the participants [63]. Game-based approaches have been found to improve problem solving and increase treatment adherence when treating patients with psychosis. The findings of this study encourage the development of game-based treatments for co-occurring SUD and psychosis. Furthermore, CBT has been widely used for SUD [64, 65] and is being implemented more frequently for patients with psychosis [30, 31, 66, 67]. One study examined a CBT intervention for patients with psychosis and cannabis use [68]. The study showed greater reduction in cannabis use and positive symptoms, as well as improved functioning in the CBT group. These findings highlight the importance of improving access to CBT for patients with psychosis and co-occurring SUD as well as developing specific CBT interventions for these patients [69].

A particular strength of this study is, that the influence of SUD measured was an active SUD during the same year and therefore during or close to the treatment period. Also, the multicentre design allowed a better generalisability of the results even though the sample size was small. To confirm efficacy and long-term outcome, further studies with larger samples are needed. It will be important for future studies to include patients with and without SUD. Also, measuring outcomes on substance use will allow us to further test the hypothesis that specific treatment for psychosis is also effective for patients with coexisting SUD.

There were some limitations in this study. We did not have any information available on the duration of disease or treatment, nor on the number and duration of hospitalisations. This would have also played an important role in influencing insight and therefore delusional belief. The data collected did not differentiate between different psychotic disorders, which may have influenced the outcome. However, the majority (around 80% in both groups) of patients were diagnosed with schizophrenia. The number of patients was particularly limited for the SUD group. It is possible that the presence of SUD was undervalued for some patients. This could be explained by two factors. First, patients were recruited in psychiatric facilities, while part of patients with SUD and comorbid psychotic disorders received their treatments in services for addictive disorders. Second, we systematically assessed current SUD and not lifetime SUD which probably contributes to lower figures. We do not have information on the severity of SUD as this was a secondary analysis and the presence of SUD was examined later using the information from the MINI. The diagnosis of SUD at study entry did not exclude a possible SUD in the patients' history. As the patients chose to participate in the group intervention and study, it limits the possible number of patients with severe SUD. Patients with more severe disorders are known to have more difficulties accessing treatment [70, 71]. They are also more likely to be enrolled in addiction programs rather than specialised psychiatric treatment programs. As the information was not available, we did not control the effects for opioid substitution or other SUD treatments. As SUD was not part of the original research question, substance use was only investigated at the beginning of the program and not in the follow-up exams. We therefore have no further information about the change of specific substance use habits in the course of treatment. It is therefore not possible to describe changes in SUD related behaviours during treatment. It is however possible, that the treatment offered might also improve outcomes for SUD even though these are not specifically targeted and should be assessed in further studies. In this sample, the symptom levels did not differ significantly between SUD and No SUD patients at baseline. This might be a reason that, in our sample, SUD did not impact treatment outcomes. Further studies on larger samples would be helpful to confirm these findings. And even though we have follow-up measures at nine months we do not have long-term outcomes to show if these are of lasting nature.

Conclusions

The presence of SUD at baseline does not seem to influence treatment outcomes over time concerning the three dimensions of delusional beliefs as measured by PDI-21. Therefore, specialised programs for psychotic disorders can be as effective for patients with concurrent SUD as for patients with psychosis only. Such treatments should be offered to patients with these comorbid disorders. It could help enhance outcomes in both areas treating the two disorders simultaneously. With one exception, the results of the sensitivity analyses matched those of the complete case analyses.

List of Abbreviations

- BPRS Brief Psychiatric Rating Scale
- MINI Mini International Neuropsychiatric Interview
- PDI Peters et al. Delusions Inventory
- SD Standard deviation
- SUD Substance use disorders

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Ethics Statement

The Ethical Committees in the respective countries approved the original study. The protocol was registered (International Standard Randomized Controlled Trial Number Register: ISRCTN37178153).
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 [5]. Informed consent was obtained from all patients included in the study.

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Conflict of Interest Statement

No financial support and no other potential conflict of interest relevant to this article was reported.
Yasser Khazaal and Jérôme Favrod are authors of the game. The research was conducted in the absence of any commercial or financial relationship that could be conceived as a potential conflict of interest.

Author Contributions

L.P. and Y.K. contributed to the conception and design of the secondary analysis. The formal analysis was performed by A.C. The first draft of the manuscript was written by L.P., T.L. and Y.K. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

Data can be made available by the corresponding author upon request.

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