ORIGINAL ARTICLE

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Therapeutic management of schizophrenia and substance use disorders dual diagnosis – clinical vignettes

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Abstract: *Patients with schizophrenia are frequently diagnosed with addictive comorbidities, and data in the literature support a 10 to 70% prevalence of this dual diagnosis. Nonetheless, substance use disorders can be missed during the initial interview with a psychotic patient, if the clinician is focused only on the more obvious manifestations. Therefore, using psychometric scales and structured interviews in patients with schizophrenia is strongly encouraged because the case manager will base his/her therapeutic decisions on quantifiable data about these patients' symptoms and functional status. Clinical management in dual diagnosis cases must address both conditions simultaneously, as the delay in the initiation of substance withdrawal treatment may hinder the recovery from a psychotic episode. An important issue is represented by the potential pharmacologic interactions between drugs administered for schizophrenia and those targeting substance withdrawal and substance dependence. Other important aspects refer to (1) the therapeutic adherence, which can influence the prognosis of both conditions, (2) the negative impact of residual psychotic symptoms and substance-related disorders over the patient quality of life and daily functioning, (3) the necessity to integrate variables like the patient's specific needs, lifestyle, and psychological resources in the therapeutic decision. These clinical vignettes are focused on clinical, biological, psychometric, and pharmacological dimensions, supporting the formulation of treatment recommendations based on monitoring both psychiatric and biological profiles.*

Keywords: *schizophrenia, substance use disorders, antipsychotics, dual diagnosis, cannabis, nicotine, alcohol dependence*

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BACKGROUND

Substance-related disorders are very common throughout the course of schizophrenia, and this phenomenon is responsible for poorer quality of life, higher impairment of daily functioning, lower rate of treatment response, lower therapeutic adherence, leading to a worse prognosis in these patients.

Prevalence of dual diagnosis (substance use disorder and psychotic disorders) ranges from 10 to 70% in a large-scale trial for schizophrenia [1].

Many hypotheses about the link between *cannabis use* and schizophrenia are still tested, cannabis being considered an independent risk factor for psychosis and a variable that may worsen prognosis in schizophrenia patients [2]. A cannabinoid hypothesis of schizophrenia has been suggested, based on the observed alteration of endocannabinoid system (abnormalities in cannabinoid type 1 receptor binding properties and modified levels of anandamide in the cerebrospinal fluid) [2]. Cannabis use was associated

with an earlier onset of schizophrenia, more severe forms of disorder, higher rates of relapse, and longer hospitalizations [3-5]. Longitudinal studies report that cannabis use in childhood and adolescence doubles the risk of psychosis onset later in life, which supports a causal role of this drug in the development of schizophrenia [6]. Certain alleles of the type 1 cannabis receptor gene (CNR1) may confer susceptibility to schizophrenia [7].

Also, the overlap of *nicotine dependence* and schizophrenia has been debated as a form of self-medication for schizophrenia-related cognitive deficits, based on the fact that the nicotine receptors activation increases the release of dopamine in cortical and subcortical areas [8,9]. Still, cigarette smoking decreases the bioavailability of many psychotropics that are metabolized through the CYP450 1A2 isoenzymes and consequently may diminish the clinical effect of these drugs and delay the patients recovery [10]. Multiple genes have been linked to both conditions, e.g. binding protein genes, protein modification genes, and energy production genes involved in cognitive functions and neuronal plasticity [11].

Alcohol use disorder was found in 33.7% of patients diagnosed with schizophrenia or schizophreniform disorder in the Epidemiologic Catchment Area study [12]. A dysregulation of the dopamine transmission has been suggested as common neurological basis, but shared genetic vulnerability factors have also been investigated (e.g. KPNA3, or alcohol dehydrogenase variants) [13-16]. A review of the current evidence for common risk factors in alcohol use disorders and schizophrenia supports a highly polygenic model, with rare penetrant alleles and frequent alleles with small effects [16].

Patients diagnosed with schizophrenia tend to abuse *anticholinergic* drugs. These agents are often used for the treatment of antipsychotic-induced extrapyramidal symptoms, and a national database analysis showed that patients with schizophrenia took 20 times more frequently antiparkinsonian agents than patients with Parkinson disease [17]. Trihexyphenidyl abusers may claim this drug improve their daily functioning and their affect, and a possible pharmacological explanation is that this agent has a structural similarity with phencyclidine [18,19]. The risk of biperiden and orphenadrine abuse was relatively small in a large database analysis [17].

CLINICAL VIGNETTES

The first patient, M.S., is a 29-year old male, diagnosed since 2015 with schizophrenia according to the DSM-5 criteria [20], currently at his third psychotic episode. He was hospitalized after he presented at the Emergency Department with delusions of persecution and auditory hallucinations ("there are people who want me dead because of my soul, they want to collect my psychic energy", "I can hear them through the walls, day and night, they are plotting against me, and they are saying bad things about my family", "They are forcing me to do evil things, like cursing strangers with no reason"). These manifestations led to changes in his behavior, he became reclusive, didn't go out of his house for weeks and spoke with his family only by phone, refusing to see them ("I can protect them if I'm not seen with them"). He recently abandoned his job as a salesman and didn't want to see her girlfriend anymore because of the belief that she was in cahoots with the persecutors who want him dead.

The pharmacological history in this case included olanzapine 20 mg/day as the main treatment for his first psychotic episode. After hospital discharge, he received the same antipsychotic for 8 months, then he dropped out and relapsed after about 6 months. The overall clinical status during the second admission was similar to the first episode of psychosis, with persecutory delusions and auditory hallucinations (both conversing and imperative voices) and induced defensive behavior- the patient refused to go out by himself because of the fear of being watched and plotted against. Olanzapine was re-initiated, but shortly after this the patient was switched on aripiprazole 30 mg/day due to concerns related to his metabolic status (240 mg/dl for the total cholesterol, 150 mg/dl for LDL-cholesterol, and 250 mg/dl for triglycerides). The evolution was favorable during the hospitalization and the patient was recommended to work in a controlled environment and to participate in occupational therapy. However, after 7 months he

discontinued treatment and soon relapsed, so that a new hospitalization was required. This time the patient was stabilized on aripiprazole, but for the maintenance phase the long acting injectable form of aripiprazole 400 mg every 4 weeks was selected, in order to diminish the risk of therapeutic non-adherence.

The patient was also diagnosed during the current psychotic episode with alcohol use disorder, moderate, based on the DSM-5 criteria, admitting a daily intake of 8 drinks, consisting mainly in beer and wine for more than 12 months. Also, he is smoking 20 cigarettes daily, with a value of 10 pack-year. Biochemistry panel reflected the liver damage, with values for gamma-GT, GOT and GPT of 156 U/l, 70 U/l, and 67 U/l, respectively. No abnormalities were detected on his chest X-ray and abdominal ultrasound exam (except for hepatic steatosis).

The psychological evaluation realized during the initial visit for the third episode showed a 98 score on PANSS [21], with high values on both positive and negative sub-scales. CRDPSS [20] score was 17, based mainly on hallucinations, delusions and abnormal psychomotor behavior. AUDIT [22] score was 14, reflecting a moderate risk of harm related to the alcohol use, and the severity of nicotine dependence was high, as supported by the FTND [23] score of 9. GAF score at admission was 45, based on symptoms severity and functional impairment, while the CGI-S score was 5, which means a "markedly ill" clinical status.

Therapeutic challenges analysis: This patient presented a history of therapeutic non-adherence which triggered two relapses. He was diagnosed with two substance use disorders (alcohol and nicotine dependence), which were not therapeutically approached during his two previous psychotic episodes, and this could be also a factor that may contribute to relapse in schizophrenia [24]. There is a lack of social and professional insertion in this case, related to both positive and negative symptoms. The patient lacks familial support and he discontinued occupational therapy. Moreover, the metabolic profile and the hepatic functional status were abnormal. All these negative prognosis factors have been evaluated by the case manager when the therapeutic strategy was formulated. Aripiprazole was preferred because of its good metabolic profile [25], and a long acting injectable formula was selected because of the more stable plasma concentrations and lower risk of discontinuation. The patient received counselling for his addictive behavior, and he participated in 4 individual sessions focused on smoking cessation and alcohol use relapse prevention. Alcohol withdrawal symptoms were mild-to-moderate and remitted after B-vitamin therapy, parenteral rehydration, and oral lorazepam 3 mg/day for 7 days, with gradual dose reduction. Naltrexone, 50 mg/day, was initiated for alcohol dependence after the withdrawal symptoms remission, and nicotine replacement therapy was suggested, but the patient refused. There are no data reported about pharmacokinetic interactions between aripiprazole and naltrexone in the literature, which supports this therapeutic recommendation.

Follow-up visits: The patient was monitored for 4 months, using psychometric instruments, in order to document psychotic symptoms, severity of addictions, and overall clinical status evolution under treatment. Global functioning improved once the psychotic positive symptoms remitted, although the negative symptoms persisted at a lower level of severity (as reflected by PANSS and CRDPSS scores).

Table 1. Psychologic evaluations during the first patient's initial visit

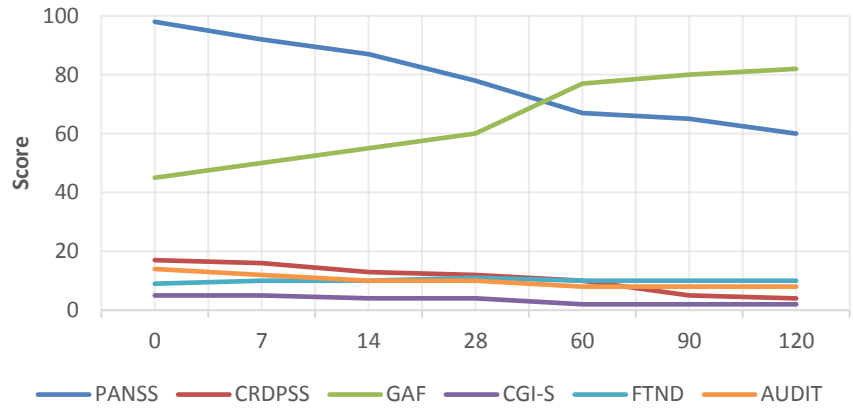
Clinical scale	Results
PANSS	98
CRDPSS	17
GAF	45
CGI-S	5
FTND	9
AUDIT- Interview Version	14

Alcohol use disorder had a favorable evolution and the AUDIT scores diminished gradually, but the nicotine dependence persisted and the mean number of cigarettes increased with 25%, while the FTND score increased with 10%. Biochemistry panel reflected an improvement of the liver status after 4 months, with values for gamma-GT, GOT and GPT of 56 U/l, 23 U/l,

and 37 U/l, respectively, and the metabolic parameters improved, also: 190 mg/dl for the total cholesterol, 120 mg/dl for LDL- cholesterol, and 170 mg/dl for triglycerides.

Conclusion: Addictive behaviors must be approached as soon as possible by the case manager in patients with schizophrenia, because the risk of therapeutic non-adherence, somatic complications, and reduced functionality is higher if these conditions are left untreated or if the appropriate treatment is delayed. In this particular case, naltrexone was efficient in the treatment of alcohol use disorder, and the patient had also significant decrease of the psychotic symptoms. However, nicotine dependence could not be addressed pharmacologically because the patient refused, and he participated only in a few counseling sessions, which led to the persistence of his substance related condition.

Fig.1. Evolution of the clinical variables during the first 4 months of treatment



The second patient, E.D., is a 30-year old female, diagnosed with schizophrenia for 6 years, currently in a partial remission, who presented to her psychiatrist asking for a therapeutic change because of galactorrhea and irregular periods. She attributed these symptoms to risperidone, which was initiated by the psychiatrist during her latest psychotic relapse, about 3 months ago.

This patient had 4 psychotic episodes since the onset of her disease at age of 22 and received for her first episode haloperidol 15 mg/day for 2 months, followed by amisulpride 800 mg/day for 10 months; for her second episode, she was treated with olanzapine 15 mg/day, for 16 months; during her third episode she received haloperidol 20 mg/day for the acute phase, and again olanzapine 15 mg/day for an indefinite period of time, and for the last episode she received risperidone 6 mg/day maintenance dose. Changes in the antipsychotic regimen were determined by adverse events- extrapyramidal symptoms during haloperidol treatment, hyperprolactinemia during amisulpride administration, and weight gain during olanzapine therapy.

This patient presented also criteria for nicotine and cannabis use disorder, both of moderate severity, according to the DSM-5 criteria. She was on cannabis for more than 2 years, with very few short periods of abstinence, and regarding nicotine use she admitted she was smoking 15 cigarettes daily for at least 8 years. She admitted she did not recognized cannabis addiction in front of her psychiatrist until the current visit. She was never offered nicotine replacement therapy or any other type of treatment targeting nicotine dependence.

The psychological evaluation during her third episode sh owed a PANSS score of 69, with low values on both positive and negative sub-scales. CUDIT-R [26] score was 16, supporting severe cannabis dependence, and the severity of nicotine dependence was high, as reflected by the FTND score of 7. GAF score at

admission was 60, based on symptoms severity and functional impairment, while the CGI-S score was 4, which means "moderately ill" clinical status. EuroQoL (EQ-5D-5L) [27,28] visual analogic scale score was 67, which seems to be correlated more with her substance-related symptoms than with her psychotic manifestations. Quality of life domains that seemed more affected by her current status were anxiety/depression (a score of 4) and usual activities (a score of 3).

Her somatic status was good, with no abnormalities on CBC or serum biochemistry panel. Also, her ECG and chest X-ray didn't suggest any abnormalities.

Therapeutic challenges analysis: This patient has a history of adverse events to several antipsychotics (haloperidol, amisulpride, olanzapine) which were severe enough to grant changes in the antipsychotic treatment. The patient received a new antipsychotic, ziprasidone 160 mg/day, which has been associated with low risk for hyperprolactinemia, weight gain, and extrapyramidal syndrome [29]. A gradual switch was preferred due to the different pharmacodynamic profiles of risperidone and ziprasidone [29-31]. ECG monitoring was initiated, and periodic measurement of metabolic parameters was continued throughout the duration of the antipsychotic therapy. The presence of cannabis use disorder raises an important question because there is no pharmacological treatment with clear evidence of efficacy in patients diagnosed with this disorder, while data about psychotherapy effects are still debatable [32]. However, gabapentin and N-acetylcysteine have been suggested as possible therapies [32], and gabapentin was preferred in this case because of its positive effect on anxiety and low risk of pharmacokinetic interactions [33]. Nicotine replacement therapy with nicotine patch 25 mg/16h for 8 weeks, followed by gradual dose reduction, combined with psychological counselling, was accepted by the patient.

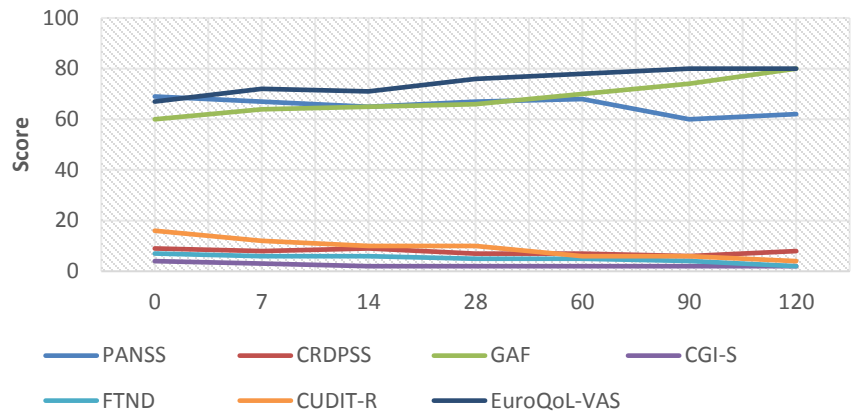
Follow-up visits: The evolution of the psychotic symptoms was favorable, as reflected in the PANSS (-10%) and CRDPSS (-11%) scores. The overall functionality increased significantly (+33%) compared to baseline, and this improvement seems related to the decrease in both FTND and CUDIT scores, with 71% and 75%, respectively. Also, the quality of life improved, both on the visual analogic scale (+17%), and on its subscales (depression/anxiety -50% and usual activities -33%). The Clinical Global Impression-Severity improved with 50%, and the patient was considered after 4 months "borderline mentally ill". Minimal QTc prolongation was detected on ECG after 4 months (+1.3%), but it didn't reach the level of significance (considered to be 460 msec in women, after correction with Fredericia's formula). No metabolic abnormalities were detected during the monitoring period, and the BMI decreased with 2.1% compared to baseline.

Conclusion: Targeting the cannabis and nicotine use disorders may improve the overall functionality and patient's quality of life, reducing further schizophrenia-associated symptoms, like depression, apathy, anhedonia or anxiety. In this case, the patient was compliant to the therapeutic suggestions, and participated in counselling sessions focused on substance use relapse prevention, while being adherent to the pharmacologic treatment. Her evolution was favorable and the therapeutic switch from risperidone to ziprasidone was well tolerated. No pharmacokinetic interactions were anticipated between the treatment for nicotine use disorder (replacement therapy), cannabis use disorder (gabapentin) and schizophrenia (ziprasidone).

Table 2. Psychologic evaluations during the second patient's initial visit

Clinical scale	Results
PANSS	69
CRDPSS	9
GAF	60
CGI-S	4
FTND	7
AUDIT – R	16
EuroQoL	
Visual analogic scale	67
Mobility	1
Self-care	2
Usual activities	3
Pain/discomfort	2
Anxiety/depression	4

Fig.2. Evolution of the clinical variables during the first 4 months of treatment



The third patient, S.G., was diagnosed for the first time with acute psychotic disorder 3 months ago. Her symptoms at hospital admission consisted in psychomotor agitation, grandiose ("I am very powerful, and I can make any wish come true, like Santa Claus, only better") and persecutory ("there is a group of forces trying to kill me and take my powers") delusions, auditory and visual hallucinations ("I can hear them talking about me and trying to make me feel miserable… they are cursing me and telling lies about me and my family", "They are moving through the light, I can see them… they are like some green shadows"), disorganized behavior, and diminished emotional expression. She was 27 years old when she was first admitted in hospital, and her psychotic symptoms had an insidious onset over at least 4 months. First, she was initiated on risperidone 6 mg/day, and her response was good, but discontinued oral treatment because she had to take this drug twice a day. The patient developed positive symptoms of psychosis after one month of no treatment, and she was readmitted in the Psychiatry Department. The selected drug for clinical stabilization was risperidone because of her previous good response. She was informed that a long acting injectable form of this antipsychotic exists, which requires administration every two weeks. Also, she was informed that paliperidone, the active metabolite of risperidone, has two long acting injectable formulations, with administration of one dose every 4 weeks, and after stabilization, the drug may be administrated every 12 weeks. She agreed to be initiated on paliperidone long acting after stabilization of acute symptoms.

The patient was smoking 30 cigarettes daily, with a value of 9 pack-years. She fulfilled the DSM-5 criteria for nicotine use disorder and accepted treatment for this condition. She received nicotine replacement therapy, but she declined the invitation to join a group therapy focused on abstinence.

Her ECG was normal, as were chest X-ray, cerebral CT-scan, CBC and serum biochemistry panel. The toxicology exam was also negative.

Table 3. Psychologic evaluations during the third patient's initial visit

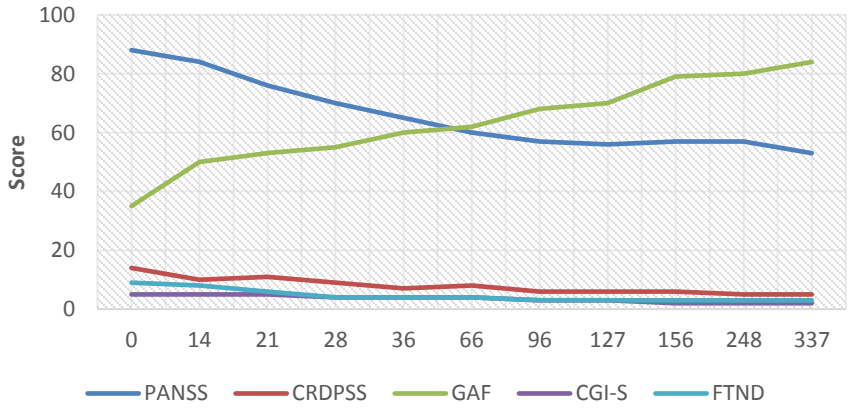
Clinical scale	Results
PANSS	88
CRDPSS	14
GAF	35
CGI-S	5
FTND	9

Therapeutic challenges analysis: This patient is still in the early phase of disease, as her diagnosis of schizophrenia was just established. She met the necessary criteria for this diagnosis- time (more than 6 months including pre-hospitalization period of active symptoms), clinical manifestations, functionality, and differentials. The challenge is to select a treatment

regimen that could be more readily accepted by a young and active person (she has to travel often because she has contracts with different enterprises), while targeting both schizophrenia and nicotine addiction symptoms. One advantage in this case is the insight of the patient and her willingness to continue the treatment. She understood the therapeutic options her psychiatrist presented, and she has chosen the treatment which allows her less time for administration and medication-supplying procedures (visits to her GP, treating psychiatrist, and local pharmacy). Therefore, paliperidone was considered the most appropriate option for her, and after stabilization with oral medication, she was switched on paliperidone palmitate (PP1M) 100 mg monthly as maintenance dose for 4 months, and paliperidone palmitate (PP3M) 350 mg every 3 months after 4 months. Regarding her nicotine use disorder, she received 25mg/16 h nicotine patches and nicotine spray administered prn, in case of withdrawal symptoms, with gradually dose reduction, and termination after 3 months. The nicotine spray was recommended because the patient is a heavy smoker, and because she had no asthma, chronic sinusitis, or other related diseases. Paliperidone is not a substrate for CYP1A2, therefore its plasma concentrations are not expected to be modified by cigarette smoking, in case substance use disorder treatment fails.

Follow-up visits: The evolution of psychotic symptoms was favorable, as reflected in the PANSS and CRDPSS scores, which decreased with 40% and 65%, respectively. The favorable trend maintained even after switching on the long-acting formulae (PP1M and PP3M). The slower rate of improvement after day 36 is related to the stabilization of the clinical status, which is a condition for switching on long-acting antipsychotic formula. The patient reported that she could return to her job after 6 weeks of treatment and her professional performances were fair. The cigarette use declined during the first 4 weeks, but she admitted she smoked during nicotine replacement therapy and after its discontinuation. Therefore, after 11 months her FTND score reflected a moderate dependence. She refused a new trial of nicotine replacement therapy and counselling sessions, as she states “smoking is not a problem for me anymore… I’m only smoking when I’m feeling nervous”. Her BMI increased with 3.5% compared to baseline, but no significant alterations in plasma lipids, blood glucose, hepatic enzymes or QTc were reported.

Fig.3. Evolution of the clinical variables during the first 11 months of treatment



CONCLUSIONS

In young patients who experience first episode of psychosis establishing therapeutic relationship could be a difficult challenge. Communication between the psychiatrist and the patient is crucial in order to assure an adequate level of therapeutic adherence. The psychiatrist should consider the lifestyle of the patient, her psychological resources and specific needs, and to

formulate the most appropriate therapeutic strategy. In this case a long-acting formula of an atypical antipsychotic was preferred because of the active lifestyle of the patient, and her expressed preference for a treatment which could be easily administered. The treatment for nicotine dependence has been a challenge, as the patient did not quit completely smoking, but only diminished it. Paliperidone could be useful in patients who smoke because it is not metabolized through CYP1A2, and its plasma concentrations remain stable even if this isoenzyme gene is induced by the polycyclic aromatic hydrocarbons of the tobacco smoke [34].

Abreviations list

AUDIT = Alcohol Use Disorders Identification Test
BMI = Body mass index
CBC = Complete blood count
CGI-S = Clinical Global Impression- Severity
CRDPSS= Clinician-Rated Dimensions of Psychosis Symptoms Severity
CUDIT-R = Cannabis Use Disorders Identification Test – Revised
EuroQoL 5D-3L= EuroGroup Quality of Life Scale
FTND = Fagerstrom Test for Nicotine Dependence
GAF = Global Assessment of Functioning
PANSS = Positive and Negative Syndrome Scale
PP1M = paliperidone palmitate with monthly administration
PP3M = paliperidone palmitate administered every 3 months
prn = *pro re nata*

Disclaimer

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