International Journal of Dual Diagnosis
2016; 1(1): 9-13
http://www.sciencepublishinggroup.com/j/ijdd
doi: 10.11648/j.ijdd.20160101.12

Review Article

Current Tendencies in Psychopharmacology of Dual Psychosis

Portilla Fernández A.[1], García Nicolás M.[2]

[1]Mental Health Net, Department of Psychiatry, Pamplona, Navarra, Spain

[2]Mental Health Net, Department of Psychiatry, Tudela, Navarra, Spain

Email address:

almudena.pf@gmail.com (Portilla F. A.), mcgn6279@hotmail.com (García N. M.)

[*]Corresponding author

To cite this article:

Portilla Fernández A., García Nicolás M. Current Tendencies in Psychopharmacology of Dual Psychosis. *International Journal of Dual Diagnosis*. Vol. 1, No. 1, 2016 pp. 9-13. doi: 10.11648/j.ijdd.20160101.12

Received: March 3, 2016; **Accepted**: March 11, 2016; **Published**: April 14, 2016

Abstract: The treatment of people suffering a Dual psychotic disorder is a real challenge for the clinical staff. MAny of clinical considers this disorder as very severe because patients presents a wide range of symptoms with a high intensity, adherence to treatment is very low and many tmes is necessary to employ the psychiatric admissions as only way to treat this problema. We carry outa review of recent publiciations about psychopharmacological and psychological treatment, citing some international guide about wich are te most effective treatment of this kind of patients

Keywords: Dual Psychosis, Psychopharmacology, Long Acting Antipscyhotic Treatment

1. Prevalence of Substance Abuse in Schizophrenia

It's well known that substance abuse is a very common comorbidity in patients suffering of schizophrenia. In fact, lifetime prevalence of substance abuse in these patients is estimated to be nearly 50%, which is threefold compared to general population prevalence. The most common abuse substances among schizophrenic patients are: alcohol (20-60% of patients) and cannabis (12-42%); followed by cocaine (15-50%) and amphetamines (10-23%). (1)

This high drug use rate in this population of patients has some more consequences than it has in general population. Some of the most important are an increased risk of developing the disease in vulnerable individuals, earlier onset of the symptoms than in non abuser patients, worse outcome (prolonged psychosis, psychosis relapses…), lower treatment compliance, higher frequency of violence episodes, homelessness, medical comorbidities (including HIV infection), greater use of crisis oriented services, and higher cost of care. (2)

Several studies have been done, aiming to analyze the characteristics of patients with first episode schizophrenia related with substance use (3). These studies include early psychosis schizophrenia spectrum disorders and affective psychosis. In all of them, similar results were found: on the first place, it was observed that a half of the patients with first episode schizophrenia had a history of cannabis abuse or dependence, while a third of them had a current cannabis use disorder. Same results and proportions were observed for alcohol abusers. Regarding cocaine, amphetamine, barbiturates and other drugs, there was a smaller proportion of user patients, but still significant. It's been also observed how traditional parallel treatment approaches were ineffective and resultant in treatment non adherence and dropout.

All of this gives clear evidence that these patients need integrated treatments, specially designed to target co-occurring mental and substance use disorders concurrently. Nevertheless, the existing studies on specialized substance abuse treatments did not demonstrate better rates of reduction of abstinence symptoms than the patients who did not receive specialized treatment for abstinence.

Studies conclude that a significant proportion of clients who were using alcohol or other drugs tend to reduce the substance use because of the traumatic experience of the first episode

and the education that they receive about preventing relapses, without a specific structured program for the substance use disorder.

Reasosns to High Rates of Substance Abuse in Schizophrenia

There are some hypotheses trying to explain this fact. Some of the most important are the ones following.

-Self medication hypothesis

There are several patients who use substance aiming to reduce psychiatric symptoms or medication side effects. In the case of patients who had a SUD prior to schizophrenia onset, this hypothesis doesn't seem to explain the high rate of SUD preceding the debut. (4)

-Common biological vulnerability hypotheses

This hypothesis involves three neurobiological pathways: dopaminergic system, endorphins and endocannabinoid system.

From a neurobiological point of view and concerning the dopaminergic system, dopamine neurotransmitter has been classically associated with the reinforcing effects of drugs of abuse and may have a key role in triggering the neurobiological changes associated with addiction. It's very common to find an altered dopamine reward system function, together with genetic alterations in both disorders, substance use disorder and schizophrenia patients. (4)It's been suggested that schizophrenic patients with SUD may be carriers of the DRD2 Taq1 A1 allele, and/or other Reward Deficiency Syndrome polymorphisms, so that they have a hypodopaminergic reward function. (4)

On the other hand, based on previous research, a plausible mechanism for alcohol seeking in schizophrenia with SUD may be deficiency of gamma type endorphins that has been linked to schizophrenic type psychosis. Alcohol seeking behavior in schizophrenic patients may serve as a physiological self-healing process, linked to the increased function of gamma endorphines by reducing abnormal dopaminergic activity in the nucleus accumbens. (4)

Regarding the roll of endocannabinoids on schizophrenia genesis, it's possible that alterations affecting the cannabinoid CB1 receptor binding in corticolimbic regions could be related to schizophrenia. It must also be taken into account that the endogenous cannabinoid system is altered in schizophrenia. (5)

2. Psychopharmacological and Psychological Treatment for Psychosis in Patients with Substance Use Disorder

It's has been demonstrated that a better treatment compliance carries more positive clinical results, not only regarding psychiatric symptoms, but also substance dependence and psychosocial activity (including less criminal behavior). This is why, when treating this type of patients, issues such as effectiveness, tolerability, easy posology, and supervision must be specially taken into account. (1)

In a recent study, Ben-Zeev et al. (19) have proposed to develop some program consisting on a team of mobile interventionists specifically trained on how to engage this patients via mobile. They suggest this system could be an effective way to strengthen service delivery models, improve patient outcomes, and reduce costs.

There are many challenges in research regarding pharmacological treatment in dual pathology. This is mainly because most clinical trials and recommendations in schizophrenia do not take into consideration substance use. This is because patients with comorbid substance use have usually been excluded from most antipsychotic trials. As a consequence, there is not much available information on this particular clinical population so it's difficult to obtain clear data. However, antipsychotic treatment appears to be as efficacious in this population as it is in non substance users.

There are some general principles of pharmacological treatment in dual psychosis that must be taken into account: First of all, there's usually a poor compliance, lower than in patients with no substance use disorder. This could be partly explained by the higher rates of adverse side effects they experience, specially extrapyramidal effects, which we must also have present when we treat with these type of patients. There's also a higher risk for several events, such as pharmacodynamic and pharmacokinetic interactions; increase of the craving symptoms mediated by classic antipsychotics in cocaine users, specially in long-term prescription; and potential increase of the euphoria due to this substance. (1)

In addition to all of this, it's always important that clinicians pay special attention to comorbid medical conditions such as hepatic, infectious or cardiac diseases that may increase pharmacological toxicity.

The current studies on this dual pathology are very poor, with many methodological limitations such the lack of placebo arms, small sample sizes or limited drug screen procedures. Also, in most of them, the effects of drugs weren't exhaustively analyzed. Some important clinical variables such as illness duration and SUD onset (prior or after schizophrenia onset) were not often considered in the statistical analysis.

In a study performed by Grau-López et al. (15), they evaluated 107 patients with Axis I comorbidity diagnosis with substance dependence, and recorded the prescribed medications. In the results, they observed that the pharmacological groups prescribed were antipsychotics followed by antidepressants, antiepileptics, anxiolytics, alcohol-aversive drugs, methadone, lithium, and naltrexone. Older patients were found to have a higher number of prescribed medications. Patients diagnosed with a dual psychotic disorder were prescribed a larger number of pharmacological agents than patients with a mood disorder or an anxiety disorder.

In another study from India (16), the authors found that atypical antipsychotics were commonly used for comorbid schizophrenia and SUD. They observed no difference between risperidone and olanzapine, but clozapine showed a distinct advantage in reducing psychotic symptoms as well as substance abuse (including smoking). They also concluded

that quetiapine is beneficial in dually diagnosed patients, particularly in those using alcohol, cocaine and amphetamine. A combination of naltrexone and sertraline was found to be effective in patients with depressive disorder and alcohol dependence. There's no clear evidence of the effectiveness of atomoxetine in patients with comorbid adult attention-deficit/hyperactivity disorder on decreasing substance abuse yet.

Some other studies (17) have suggested that, combining aripiprazole and topiramate may be effective in patients with a dual diagnosis of opioid dependency and schizoaffective disorder. Others (18), conclude that both clozapine and ziprasidone could have beneficial effects in the treatment of cannabis use disorders in psychotic patients.

On the other side, the hypothesis that antipsychotic treatment might contribute to increase drug addiction in patients with schizophrenia has also been defended (20). It's been suggested that some treatment strategies that are currently being used with atypical antipsychotics could actually induce forms of neural plasticity that would facilitate the ability of drugs and reward cues to gain control over behavior, contributing to compulsive drug seeking and drug taking behaviors in vulnerable schizophrenia patients.

3. Typical or Atypical Antipsychotics: Select the Best Options

Dopamine increase in nucleus accumbens is related wit drug reward, consuming thoughts and craving. Atypical antipsychotic treatment blocks this process. Its anti-D4 and anti 5-HT 2c actions have anti-consuming functions, such as lowering sensation seeking and impulsivity. (1)(Table 1)

There are several factors contributing to increase substance use in these patients, such as positive and negative symptoms, subjective dysphoria, cognitive impairment, extrapyramidal symptoms, anhedonia or psychopathic traits. Most of them tend to remit with D2 and 5HT2 agonist atypical antipsychotic treatment.

Table 1. *Principal atypical antipsychotic receptors and their relevance in dual pathology.*

	D_1	D_2	D_3	D_4	5-HT_{2A}
CLOZ	++	++		+++	++
OLANZ	++	++		++	+++
QUETP	+	+		+	++
RIS/PAL	-	+++		++	++++
ZIPRAS	+	+++		++	++++
AMSUL	-	+++	+++	-/+	-
ARIPIP		++			++

5HT2A receptor blockade reverts the effects of D2 blockade; D4 receptor blockade lowers new sensation seeking and drug use in schizophrenic patients; and D1 blockade lowers the reinforcing properties of drugs, so patients tend to use more drugs to compensate this effect.

According to the current clinical practice, there are some issues:

- Does a low dose of typical antipsychotics contribute to substance misuse?
- Are atypical antipsychotics better than typical in reducing substance misuse and/or treating the comorbidity, and if so, why?
- Is clozapine superior to other atypical antipsychotics?

It's seems obvious that some specifically designed randomized controlled trials to look at this comorbidity are required. Meanwhile, general recommendations say that the same pharmacological practice as in non SUD patients should be used because of the lack of clear data.

It´s necessary to contemplate that more extrapyramidal effects are reported when using typical antipsychotics than when using atypical ones in this population. In some studies (1), atypical antipsychotics have demonstrated higher efficacy, as well as specific efficacy in preventing relapses on the abuse of substances than typical ones. However, these results have not been replicated in other studies. Also, typical antipsychotics have been associated with increased craving symptoms in cocaine abusers in some studies.

In terms of efficacy, clozapine has demonstrated superiority explained by a positive effect on the disrupted dopamine-mediated reward brain system through its multiple actions on neurotransmitter systems.

In terms of reduction of substance use relapses, clozapine was also the best option, followed by olanzapine and risperidone.

In a randomized controlled trial, olanzapine has demonstrated superiority in reducing the cocaine craving respect to haloperidol but didn't show superiority in terms of positive urine toxicology or in the PANNSS scores. Nevertheless, in other studies these results were no replicated in the comparison.

4. Current Guidelines of Assesment and Management of Psychosis Associated to Comorbid Substance Abuse: A Review

-NICE guidelines 2011- (10)

The principal conclusions of this guide are the following:

-First of all, psychosis must be recognized in patients with a substance use disorder. Secondly, as in every patient, we should try to build a good therapeutic alliance.

-It's very important to labour motivation on these patients.

-Mental Health Services should work together with drug addiction support services and with primary care.

-Patients should not be excluded because of the substance use disorder.

-Antipsychotics should be used according to the guideline on schizophrenia (NICE clinical guideline 82) or bipolar disorder (NICE clinical guideline 38) because there is no evidence for any differential benefit for one antipsychotic over another in people with psychosis and coexisting substance misuse.

-In the same way, depot/long-acting injectable antipsychotics are used according to the guideline on schizophrenia (NICE

clinical guideline 82) in managing covert non-adherence with treatment for psychosis, and not as a specific treatment for psychosis and coexisting substance misuse.

-When prescribing medication for adults and young people with psychosis and coexisting substance misuse, it's important to pay special attention to some issues.

On the first place, we must take into account the level and type of substance misuse, specially of alcohol, as this might alter the metabolism of prescribed medication, decrease its effectiveness and/or increase the risk of side effects (for example, anticholinergic effects potentiated by Cannabis or extrapyramidal effects potentiated by cocaine).

Secondly it's very important to warn the patient about potential interactions between substances of abuse and prescribed medication.

It's necessary to discuss the problems and potential dangers of using non-prescribed substances and alcohol to counteract the effects or side effects of prescribed medication.

-World Federation of Societies of Biological Psychiatry (WESBP) Guidelines

These guidelines affirm that clozapine seems to be effective on the reduction of craving and substance intake in patients with a dual diagnosis of schizophrenia and alcohol use disorder (Catergory of Evidence B, Level of Recommendation 3) and other substance use disorder (Catergory of Evidence C3, Level of Recommendation 4).

However clinicians should take into account that the high level of non-compliance in this patient group assessment period when initiating treatment, again, may limit the use of clozapine.

Special caution is required in patients with alcohol use disorders as they are at risk to develop diseases of the blood-forming system (such as macrocytic anaemia, but also pancytopenia) or bone marrow suppression that may increase the risk for clozapine-induced agranulocytosis. Furthermore, comorbid alcohol use disorder may potentiate clozapine-induced cardiac toxicity.

Some antipsychotics appear to be effective in patients with a dual diagnosis of schizophrenia and alcohol use disorder (Catergory ofEvidence C3, Level of Recommendation 4) for reducing of craving and substance intake. Other antipsychotics (both typical and atypical antipsychotics) showed limited positive evidence in schizophrenia patients with cocaine use disorder (Category of Evidence B, Level of Recommendation 3) for the reduction of craving and substance intake.

An inconsistent superiority of second generation antipsychotics compared to first generation antipsychotics in the reduction of craving and the level of substance use can be assumed (Category of Evidence C3, Levelof Recommendation 4).

Due to the high non-compliance in dual diagnosis patients the use of long-acting injectables is specially useful (Category of evidence C3, Level of Recommendation 4).

5. Injectable Antipsychotics and Others

While more research is needed, long-acting antipsychotics should be considered as an important option in this population due to their poor compliance and seeking a reduction on relapses and number of hospitalizations.

-In a randomized controlled trial comparing clozapine vs ziprasidone (7) in patients with schizophrenia and cannabis abuse, cannabis use was reduced in both groups during follow up. Clozapine treatment was more efficacious in positive symptoms but showed more side effects and poorer compliance.

-Aripiprazole in schizophrenia with cocaine dependence: A pilot study suggests possible aripiprazole effects in lowering both desire for and the use of cocaine in comorbid schizophrenia subjects (9).

In our group (Navarre-Spain) we have treated a sample of 19 subjects with schizophrenia and substance use disorder with paliperidone palmitate. They had been previously treated with oral atypical antipsychotics and keeping active consumption of substances. After switching medication, 8 of them were free from substance intake and with an excellent control of the relapse rate and positive symptomatology (11).

6. Conclusions

There's a lot of controversy regarding dual psychosis treatment strategies. There are very few studies regarding this specific area, as these patients are more complicated than the ones not using drugs, so they're usually excluded of the studies for this reason. It seems clear that further investigation in this issue is needed in order to provide these patients good medical care, and that integrated intervention is the choice of treatment for patients with dual diagnosis. But in any case, it's demonstrated that antipsychotic treatment is necessary in these patients and equally effective than in the ones not suffering from a comorbid SUD. Atypical antypsichotics have shown more beneficial effects in lowering sensation seeking behavior and substance abuse. Long acting injectable antipsychotics could be a specially good option in these patients as they offer an easy posology helping to increase therapeutic alliance.

References

[1] Sepede G, Lorusso M, Spano MC, Di Iorio G, Martinotti G, et al.(2014) Substance Use in Schizophrenia: Efficacy of Atypical Antipsychotics. J Schizophr Res, 1(1): 1-12.

[2] Lisa Dixon. (1999) Dual diagnosis of substance abuse in schizophrenia: prevalence and impact on outcomes. Schizophrenia Research. Volume 35, Supplement 1, Pages S93–S100.

[3] Jennifer p. Wisdom. (2011). Substance Use Disorder Among People with First-Episode Psychsis: A systematic Review of Courseand Treatment. Psychiatric services (Washington DC)., pp 1007-1012.

[4] Blum K, Oscar Berman M. (2014). Hypothesizing dopaminergic genetic antecedents in schizophrenia and substance seeking behavior. Med Hypotheses: 606-14.

[5] Fernandez-Espejo E, Viveros MP, Núñez L. (2009). Role of cannabis and endocannabinoids in the genesis of schizophrenia. Psychopharmacology (Berl): 531-49.

[6] The World Journal of Biological Psychiatry, 2015; 16:142-170 (TREATMENT GUIDELINES) World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia. Part 3: Update 2015 Management of special circumstances: Depression, Suicidality, substance use disorders andpregnancy and lactation

[7] Schnell T, Koethe D, Krasnianski A, Gairing S, Schnell K, Daumann J, Gouzoulis-Mayfrank E. (2014) Ziprasidone versus clozapine in the treatment of dually diagnosed (DD) patients with schizophrenia and cannabis use disorders: a randomized study. Am J Addict: 308-12.

[8] Koola MM, Wehring HJ, Kelly DL. (2012). The Potential Role of Long-acting Injectable Antipsychotics in People with Schizophrenia and Comorbid Substance Use. J Dual Diagn.; 8(1): 50-61.

[9] Beresford TP, Clapp L, Martin B, Wiberg JL, Alfers J, Beresford HF. (2005) Aripiprazole in schizophrenia with cocaine dependence: a pilot study. J Clin Psychopharmacol. 25(4):363-6.

[10] Psychosis with coexisting substance misuse: Assessment and management in adults and young people NICE guidelines [CG120] Published date: March 2011.

[11] Núnez Domínguez, García María del Carmen. (2014). Palmitato of paliperidone in dual pathology. A retrospective study. Adicciones Intepsiquis 2014. Congreso Virtual de Psiquiatría.

[12] Ikeda T, Koike J, Kouda M, Inamoto A, Morota N. (2014). Investigation of community support measures for patients with comorbid substance use disorder and_psychotic_disorder: nationwide survey of drug addiction rehabilitation centers. Nihon Arukoru Yakubutsu Igakkai Zasshi.

[13] Boden MT, Moos R. (2013). Predictors of substance use disorder treatment_outcomes among patients with_psychotic disorders. Schizophr Res. 2013 May

[14] Bartoli F, Scarone S, Clerici M. (2013). Risk of hospitalization among patients with co-occurring psychotic and substance use disorders: a 12-year follow-up. Riv Psichiatr. ;48(1):51-9.

[15] Grau-López L, Roncero C, Daigre C, Miquel L, Barral C, Gonzalvo B, Collazos F, Casas M. (2014). Observational study on medications prescribed to dual-diagnosis outpatients. J Addict Med.;8(2):84-9.

[16] Murthy P, Chand P. (2012). Treatment of dual diagnosis disorders. Curr Opin Psychiatry; 25(3):194-200.

[17] Bruno A, Romeo VM, Pandolfo G, Scimeca G, Zoccali RA, Muscatello MR. (2014). Aripiprazole plus topiramate in opioid-dependent patients with schizoaffective disorder: an 8-week, open label, uncontrolled preliminary study. Subst Abus.; 35(2): 119-21

[18] Schnell T, Koethe D, Krasnianski A, Gairing S, Schnell K, Daumann J, Gouzoulis-Mayfrank E. (2014). Ziprasidone versus clozapine in the treatment of dually diagnosed (DD) patients with schizophrenia and cannabis use disorders: a randomized study. Am J Addict.;23(3):308-12

[19] Ben-Zeev D, Kaiser SM, Krzos I. (2014). Remote "hovering" with individuals with psychotic disorders and substance use: feasibility, engagement, and therapeutic alliance with a text-messaging mobile interventionist. J. Dual Diagn. 10(4):197-203.

[20] Samaha AN. (2014). Can antipsychotic treatment contribute to drug addiction in schizophrenia? Prog Neuropsychopharmacol Biol Psychiatry. 3;52:9-16.