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Research Article

Substance Use in Schizophrenia: Efficacy of Atypical Antipsychotics

Gianna Sepede[1]*, Marco Lorusso[1#], Maria Chiara Spano[1#], Giuseppe Di Iorio[1,2], Giovanni Martinotti[1,2], Rita Santacroce[1], Rosa Maria Salerno[1], Francesco Gambi[1] and Massimo Di Giannantonio[1,2]

[1]Department of Neuroscience Imaging and Clinical Science, "G. D'Annunzio" University of Chieti, Italy
[2]Department of Mental Health, National Health Trust, Chieti, Italy
[#]Equally Contributed

***Corresponding author:** Gianna Sepede, Department of Neuroscience Imaging and Clinical Science, ITAB - Institute for Advanced Biomedical Technologies, "G. D'Annunzio" University of Chieti, Via dei Vestini 33, 66013 Chieti Scalo (CH), Italy

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Abstract

Background: Substance Use Disorders (SUDs) are common among patients with schizophrenia and dramatically worsen their outcome. In the last years, the use of Atypical Antipsychotics (AAPs) in dual diagnosis has become an encouraging clinical strategy. Aim of the present paper is to provide a systematic literature review on efficacy and safety of AAPs use in schizophrenic patients with comorbid SUD.

Methods: We searched PubMed to identify original studies pertaining the use of AAPs in treating dual-diagnosed schizophrenic patients.

Results: We found 12 papers that met our inclusion/exclusion criteria: five randomized clinical trials, two open label trials and five observational studies. 1432 schizophrenic patients, 905 of them with a comorbid SUD, were involved. Olanzapine, Risperidone and Clozapine were the most prescribed AAPs; alcohol, cannabis and cocaine the most frequent substances of abuse. None of the selected studies was placebo-controlled: AAPs were compared to Typical Antipsychotics (TAPs) or one another. AAPs resulted usually, but not always, more efficacious than TAPs on substance related problems. In those studies comparing different AAPs, clozapine showed better results than other treatments, whereas no significant differences emerged between risperidone and olanzapine. In terms of safety, AAPs were usually well tolerated.

Conclusions: Our review suggests that AAPs, in particular clozapine, olanzapine and risperidone, may be a promising therapeutic option for schizophrenic patients with comorbid SUD. On the other hand, given the limited number of randomized controlled trials and the lack of placebo arms, further studies are needed to better address this point.

Keywords: Schizophrenia; Dual diagnosis; Atypical antipsychotics; Comorbidity; Substance abuse

Introduction

Substance Use Disorders (SUDs) are common among schizophrenic subjects: their lifetime prevalence of substance abuse is nearly 50%, three times higher than general population [1], and it seems to increase over time [2,3].

The substances most commonly abused by schizophrenic patients are alcohol (20%-60%), cannabis (12%-42%), cocaine (15%-50%) [4] and amphetamines (10%-25%) [5]; moreover, a high percentage of patients are poly-drug users [6].

Substance use increases the risk of schizophrenia in vulnerable individuals [7-9] and is associated with a younger age of symptoms onset with respect to schizophrenic patients without SUD [10,11].

Many hypotheses have been suggested to explain the elevated rates of substance abuse in schizophrenia. One hypothesis involves the principle of self-medication: patients may use substances to reduce psychiatric symptoms or side effects of medications [12-14]; this may be true especially when the SUD onset follows the development of psychotic symptoms [15]. This theory, however, does not explain the high rate of SUD preceding the clinical onset of schizophrenia [16]. A more recent hypothesis is that psychosis and substance use disorder share an altered function of dopamine-mediated reward-system [17], and common genetic alterations have been suggested to explain the high prevalence of SUD in schizophrenia [18-20].

A comorbid SUD in psychiatric patients significantly worsens their compliance, functional outcome and quality of life [21, 22] and the pharmacological treatment of dual diagnosis still appears as a challenge in psychiatric practice. In the last decades, Atypical Antipsychotics (AAPs) have largely replaced Typical Antipsychotics (TAPs) in the treatment of schizophrenia [23, 24], due to their efficacy and better tolerability. Nevertheless, their use in dual-diagnosed patients is still debated [25, 26]. Aim of the present paper is to provide a systematic literature review on efficacy and safety of AAPs use in schizophrenic patients with comorbid SUD.

Methods

We searched PubMed to identify original studies pertaining the use of AAPs in the treatment of schizophrenic patients with comorbid SUD. The following search words were used, both alone and in combination: schizophrenia, atypical antipsychotics, substance use, dual diagnosis, comorbidity.

The search was conducted on June 2nd, 2014 and yielded 135

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records. Moreover, we manually checked the reference lists of the identified articles and we found 4 more potential studies, for a total number of 139 records. Inclusion criteria were the following: original articles (open label or double blind trials, prospective or retrospective observational studies) written in English, patients' age ≥ 18 years, patients affected by schizophrenia with SUD, treatment with AAPs. Animal studies, reviews, commentaries, case reports, studies not enrolling dual-diagnosed patients or not including a treatment arm with AAPs were excluded.

By reading titles and abstracts, we excluded 118 records. By reading the full texts of the 21 remaining articles, we found 12 papers meeting our inclusion/exclusion criteria, and therefore included in the qualitative synthesis (Figure 1).

Results

Our qualitative synthesis includes 12 papers, for a total number of 1432 participants affected by a Schizophrenic Spectrum Disorder (SCZ-S): Schizophrenia (SCZ), Schizophreniform (SCP) or Schizoaffective Disorder (SCA). The studies we considered were five Randomized Controlled Trials (RCT), all with active treatments as comparators [10,27-30], two Open Label Trials (OLT) [31,32], two prospective observational studies [33,34] and three retrospective observational studies [35-37].

The study duration of the clinical trials ranged from 6 to 24 weeks, whereas the observational studies duration was longer, ranging from one to six years. In nine of the studies, only data regarding SCZ-S with a comorbid SUD were reported, whereas in 3 studies [10,29,34] a group of SCZ-S without comorbid SUD was also included in the analyses. A total of 905 SCZ-S with a comorbid SUD and 527 SCZ-S without a comorbid SUD were examined.

The characteristic of the groups and the results of the studies are synthesized in Table 1 and reviewed below.

In a 12-week RCT comparing Olanzapine (OLA) to Haloperidol (HAL) in the treatment of first-episode psychoses, Green et al. [10] analysed 262 patients with SCZ, SCA or SCP. Ninety-seven patients (37%) had a comorbid lifetime substance use disorder (SUD), 20 patients (7,6%) had a current SUD and 165 patients (63%) did not report any SUD. With respect to non-abusers, patients with a comorbid SUD were more frequently males (93% vs. 75%, p<0.001), had a longer duration of untreated psychosis (19.5 vs. 12.1 months, p<0.05), more positive symptoms and less negative symptoms at baseline. Most abused substances were cannabis (28%), and alcohol (21%).

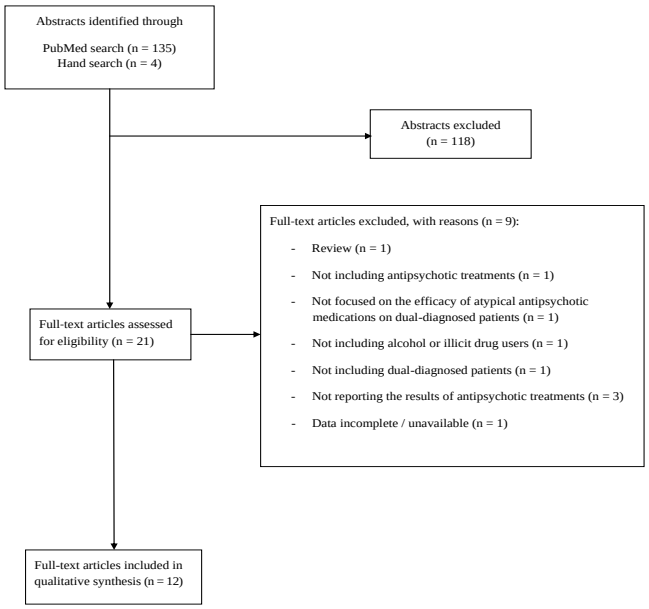

Figure 1: Flow chart of the systematic review.

After 2 to 14 days of washout, patients were randomly assigned to receive OLA (mean dose 10.2 mg/day) or HAL (mean dose 4.8 mg/day) for 12 weeks. Patients who met the following criteria were classified as treatment responders: (1) no rating >3 on items P1, P2, P3, P5 and P6 of the Positive and Negative Syndrome Scale (PANSS) [38]; (2) ≥30% reduction from baseline in PANSS total score; and (3) Clinical Global Impression (CGI) [39] severity score < 4 (moderately ill). At follow up, patients with SUD had a lower rate of compliant days (93% vs. 75%, p<0.001) and a reduced response rate (27% vs. 35%) with respect to non-SUD. When comparing the two treatment groups, the response rate among SUD patients was quite similar (OLA = 23%; HAL = 31%). On the other hand, when considering only patients with a comorbid alcohol use disorder (AUD), the percentage of responders resulted to be lower in the OLA group with respect to the HAL group (9% vs. 27%). The presence of a comorbid SUD significantly reduced the completion rate in the HAL group (51% vs. 71%, p<0.04), but not in the OLA group (77% vs. 71%, p<0.53).

Sayers and colleagues [27] conducted a 26-week RCT comparing OLA to HAL in the treatment of SCZ with comorbid current cocaine abuse. Twenty-four participants were selected, and switched from their previous therapy to OLA (N=12) or HAL (N=12) after a 2-week washout. The endpoints of the study were: (1) reduction in psychiatric symptoms, assessed with the Brief Psychiatric Rating Scale (BPRS) [40], the Scale for the Assessment of Negative Symptoms (SANS) [41] and the Scale for the Assessment of Positive Symptoms (SAPS) [41], and (2) reduction of cocaine use and craving. At the end of the study, the two treatment groups did not significantly differ in terms of study completion (58.3% in both groups), reduction in BPRS, SANS and SAPS scores and cocaine use. A significantly lower self-reported cocaine craving, assessed using a Visual Analogue Scale (VAS) was observed in the HAL group, with respect to the OLA group. When comparing tolerability profiles, the authors found higher level of extrapyramidal symptoms (EPS) in the HAL group, as measured by the Abnormal Involuntary Movement Scale (A.I.M.S.) [42].

A 6-week RCT aiming to compare OLA to HAL in the treatment of SCZ with comorbid current cocaine abuse was conducted by Smelson et al. in 2006 [28]. A total of 31 patients was enrolled and randomly assigned to receive 5-20 mg/day (mean dose 10 mg/day) of OLA (N=16) or HAL (N=15). At the end of the study, OLA showed more effectiveness in reducing the cocaine craving with respect to HAL, as measured by the energy subscale of the Voris Cocaine Craving Questionnaire (VCCQ) (Voris) [43]. On the contrary, the two groups did not significantly differ in terms of study completion and positive urine toxicology. OLA-treated patients showed lower PANSS scores with respect to HAL-treated patients, but the difference did not reach statistical significance (p=0.07).

Table 1: Summary of original studies examining the efficacy and safety of atypical antipsychotics in patients affected by Schizophrenic Spectrum Disorders and comorbid Substance Use Disorders.

STUDY	DESIGN, DURATION, AIMS AND EVALUATION INSTRUMENTS	PARTICIPANTS	ACTIVE MEDICATIONS	ALLOWED TREATMENTS	SUBSTANCE OF ABUSE / DEPENDENCE	EFFICACY	SAFETY
Green et al, [10]	Double blind, randomized, controlled trial Study duration: 12 weeks Aims: to compare OLA to HAL in the treatment of first-episode psychoses Evaluation instruments: SCID-IV, PANSS, MADRS, CGI, SAS, AIMS, BAS	262 patients with first-episode psychoses (SCZ, SCA, SCP). Age range: 16-40 years Comorbid diagnosis: - with lifetime SUD N= 97 (37%), Males: 93% - without SUD N=165 (63%), Males: 75%	OLA group (N=131) First 6 weeks: 5-10 mg/day. Second 6 weeks: 5- 20 mg/day. Mean dosage: 10.2mg/day HAL group (N=131) First 6 weeks: 2-6mg/day. Second 6 weeks 2-20 mg/day Mean dosage: 4.8 mg/day	chloral hydrate (500 to 2000 mg/day) lorazepam (1 to 8 mg/day) diazepam (5 to 40 mg/day) benzatropine or biperiden (up to 6 mg/day) propranolol (10 to 80 mg/day) procyclidine (up to 30 mg/day)	Cannabis: N=74 (28%) Alcohol N=54 (21%) Cocaine: N=17 (6%) Hallucinogens/ PCP: N=12 (5%) Opioids: N=3 (1%)	Definition of treatment responders: 1) no rating >3 on items P1, P2, P3, P5 and P6 of the PANSS; 2) ≥30% reduction from baseline in PANSS total score 3) CGI severity score < 4 Response rate: with SUD 27%; without SUD 35% OLA group (overall 31.7%): with SUD 23%; without SUD 38% HAL group (overall 34.9%): with SUD 31%; without SUD 32% Study completion: OLA group - With SUD 77% - Without SUD 71% (Fisher exact p<0.53) HAL group - With SUD 51% - Without SUD 71% (Fisher exact p<0.04)	Drop outs: OLA group - With SUD 23% - Without SUD 29% HAL group - With SUD 49% - Without SUD 29%
Sayers et al, [27]	Double blind, randomized, controlled trial Study duration: 6 months Aims: to compare OLA to HAL in reducing psychiatric symptoms, cocaine craving and abuse Evaluation instruments: AIMS, BAS, SARS,HAM-D, VAS, BPRS, SAPS, SANS, weekly urine drug screen	24 outpatients with SCZ Males: N= 23 (95.8%) Mean age: 45.9 years Comorbid diagnosis: - SUD N= 24 (100%)	OLA group (N=12): 10-20 mg/day HAL group (N=12): 10-20mg/day	Benzatropine 1mg in the HAL group	Cocaine N= 24 (100%)	Endpoints: - study completion - ≥30% reduction in BPRS score - reduction of SANS and SAPS scores - cocaine consumption reduction - cocaine craving reduction Study completion (overall N=14, 58.3%): OLA N= 7 (58.3%) HAL N=7 (58.3%) ≥30% reduction in BPRS score (overall N= 7, 29.2%): OLA N=3 (25%); HAL N= 4 (33.3%) - HAL = OLA in reducing cocaine use, SANS and SAPS scores - HAL > OLA in reducing self-reported cocaine craving (p<0.05)	Drop outs: OLA group 41.7% HAL group 41.7% A.I.M.S. scores: HAL (8.9) > OLA (3.1), p<0.05 BAS, SARS and HRSD scores: HAL = OLA

Smelson et al, [28]	Double blind, randomized, controlled trial Study duration: 6 weeks Aims: to compare OLA to HAL in reducing cocaine craving, cocaine abuse and psychiatric symptoms. Evaluation instruments: VCCQ, PANSS	31 patients with SCZ Males: N= 31 (100%) Mean age: OLA group = 42.5 years HAL group = 43.3 years Comorbid diagnosis: - SUD N=31 (100%)	OLA group (N=16): 5-20 mg/day (mean dose: 10mg/day) HAL group (N=15): 5-20 mg/day (mean dose: 10mg/day)	Psychosocial treatment Anticholinergics in the HAL group	Cocaine N=31 (100%)	Endpoints: - reducing cue-elicited craving - decreasing drug use - improving psychiatric symptoms Study completion: OLA N=8 (50%) HAL N=10 (62.5%) Results: Craving: OLA > HAL in VCCQ Energy score (p = 0.04). Other craving dimensions did not significantly differentiate the groups. PANNS score: OLA ≤ HAL (p=0.07) Positive urine toxicology: OLA= 12.5% HAL= 40% (Chi squared p=0.20)	Drop outs: OLA group 50% HAL group 37.5% (Chi squared p=0.47)
Van Nimwegen et al, [29]	Double blind randomized controlled trial. Study duration: 6 weeks Aims: to compare OLA to RIS in improving subjective wellbeing, cannabis use and craving. Evaluation instruments: SCID-IV, DDQ, OCDUS, SWN	128 SCZ, SCA or SCP Age range: 18-30 years Mean age: 25 years Males: 80% Comorbid diagnosis: - SUD N=41 (32%)	OLA group (N= 63; with SUD N= 20): 5-20 mg/day (mean dose: 11.1 mg/day) RIS group (N= 65, with SUD N=21): 1.25- 5 mg/day (mean dose 3 mg/day)	Oxazepam Biperiden	Cannabis: N=41 (32%)	End points - improving subjective well being - reducing craving and cannabis use Study completion: 78% Results: Both OLA and RIS were associated with an improved subjective wellbeing, without any between-group significant effects (SWN change p=0.85) OLA and RIS were equally efficacious on craving (OCDUS change p=0.39; DDQ reduction p=0.34) and reduction of mean number of joints (p=0.16)	Dropouts (N=31, 22%) OLA N= 20 (31.7%) RIS N= 11 (16.9%) Reasons: - adverse events (N=9): OLA N=6; RIS N=3 - lack of efficacy (N=8): OLA N=4; RIS N=4 - withdrew consent (N=10): OLA N=7; RIS N=3 - combination (N=4): OLA N=3; RIS N=1

Sevy et al, [30]	Double blind, randomized controlled trial (secondary analysis) Study duration: 16 weeks Aims: to compare OLA to RIS in reducing psychiatric symptoms and substance use. Evaluation instruments: SCID, SADS-C+PD, CGI, SANS-Hillside Clinical Trial version	49 patients with first-episode psychoses (SCZ, SCP, SCA) Age range: 16-40 years. Mean age: 21.7 years Males: N=40 (81.6%) Comorbid diagnosis: - Lifetime SUD N=49 (100%)	OLA group (N= 28): 2.5-20 mg/day RIS group (N= 21): 1-6 mg/day	Lorazepam Sertraline Divalproex sodium Benztropine Propanolol Psychoeducation treatment	Cannabis: N=49 (100%) Alcohol: N=19 (38.8%) Cocaine: N=5 (10.2%) Hallucinogens N=2 (4.1%) Opiates N=1 (2.0%) Inhalants N=1 (2.0%)	Definition of treatment response: for at least two consecutive visits 1) a rating of mild or better in the SADS-C+PD items 2) a CGI rating of “improved” or “much improved” Other end point: Substance use reduction Study completion (overall 75.5%): OLA N= 21 (75%), RIS N=16 (76.2%) (Chi squared p=0.90) Response rate: OLA N=13 (45%), RIS N=11 (54%) (Chi squared p=0.68) Both groups improved for positive symptoms (p<0.0001) and asociality-anhedonia (p=0.0002) Current cannabis use at the end of the study (32.4%) was lower with respect to the baseline (54.1%) (Chi squared p=0.049), with no between-treatment effects.	Dropouts (N=12, 24.5%): OLA N= 7 (25%) RIS N=5 (23.8%) Weight and BMI significantly increased over time (Chi squared p=0.049) in both groups Mean weight change: OLA = 11.3 kg RIS = 5 Kg Mean BMI change: OLA = 3 points RIS = 3 points
Smelson et al, [31]	Open label study. Study duration: 6 weeks Aims: to compare RIS to typical neuroleptics in reducing cocaine craving, psychiatric symptoms and relapses. Evaluation instruments: VCCQ, PANSS	18 patients with SCZ Males: N= 18 (100%) Mean Age: 43.1 years Comorbid diagnosis: SUD: N=18 (100%)	RIS group (N=8): 2-6 mg/day, mean CPZ equivalents dose: 550 mg/day TAPs (HAL, FLU, CPZ) group (N=10): mean CPZ equivalents dose: 522.9 mg/day		Cocaine N= 18 (100%)	Endpoints: - reducing cue-elicited craving - decreasing drug use - improving psychiatric symptoms Study completion: 50% TAPs N=3 (30%), RIS N=6 (75%) Results: RIS > TAPs in reducing intensity (p= 0.005) and depression (p=0.031) dimensions of craving as assessed by VCCQ A trend toward a higher reduction of PANSS global (p=0.079) and negatives (p=0.068) scores was observed in the RIS group, with respect to the TAPs group Substance abuse relapse rates: RIS N=1 (12.5%), TAPs N=7 (70%) (Fisher’s Exact Test p=0.025).	Dropouts (N=9, 50%) TAPs N=7 (70%) RIS N=2 (25%) (Fisher’s exact test p=0.15)

Rubio et al, [32]	Open label study Study duration: 24 weeks Aims: to compare long-acting injectable RIS to ZUC-depot in improving substance abuse and psychiatric symptoms Evaluation instruments: ASI, PANSS, CGI, ESRS, UKU Side Effect Rating Scale.	115 patients with SCZ Age 18-65 years Mean age: RIS group = 37.9 years ZUC group = 33.4 years Comorbid diagnosis: SUD N= 115 (100%)	RIS group (N=57): 47.2mg/15 days long-acting RIS + 3.4 mg/day oral RIS ZUC group (N=58): 200 mg/21days ZUC-depot +15 mg/day oral ZUC	Antiparkinsonian drugs	Alcohol: N=101 (87.8%) Cannabis: N=82 (71.3%) Nicotine N=81 (70.4%) Cocaine: N=30 (26.1%) Opiates N=10 (8.7%) Amphetamines N=5 (4.3%)	Outcomes: - number of positive urine test - time elapsed before the first positive urine test - ≥20% reduction in PANNS score - ≥75% attendance at SAMM program sessions Study completion: 92.2%. Results: - Relapse for substances: 100% - Number of positive urine test: RIS (N= 8.7) < ZUC (N= 10.4) (p= 0.005) - PANSS scores: Negative: RIS < ZUC (p=0.008) General: RIS < ZUC (p=0.05) Total: RIS < ZUC (p=0.02) Good compliance to SAM: RIS > ZUC (p=0.001)	Dropouts (N=9, 7.8%): RIS N=3 (5.2%) ZUC N=6 (10.3%) Hospitalization due to symptoms exacerbation: RIS N=10 (17.5%) ZUC N= 11 (18.9%) EPS and UKU scores: RIS < ZUC (p=0.04) Antiparkinsonian drugs use: ZUC (48.5%) > RIS (27%) (p<0.01)
Brunette et al, [33]	Prospective observational study Study duration: 2 years Aims: to compare CLO to other antipsychotics in preventing substance abuse relapses Evaluation instruments: SCID, TLFB, ASI, Quality of life interview, BPRS, Service utilization interview, urine toxicology screens, AUS, DUS, SATS	95 outpatients with SCZ or SCA Males: N=67 (70.5%) Mean age: CLO group = 33.7 years Other APs group = 35.1 years Comorbid diagnosis: SUD, in remission for at least 6 months N= 95 (100%)	CLO group (N=25). Mean dosage at 1-year follow up: 484 mg Other group: - TAPs (N=62) - RIS (N=4) - OLA (N=4)	Mood stabilizers (N=24, 25.3%): Antidepressants (N=23, 24.2%) Benzodiazepines (N=19, 20%) A second antipsychotic medication (N=9, 9.5%)	Alcohol Cannabis Cocaine Other substances	Outcomes: - Preventing relapses to substance abuse - improving the psychiatric symptoms Study completion: - one-year follow up: 100% - two-year follow up: 67.4% 1-year follow up results: Substance abuse relapses: CLO (8%) < Other (40%) p=0.003 Day of alcohol use, AUS, DUS scores: CLO < Other (p<0.05) SATS scores: CLO > Other (p<0.05) 2-year follow up results Substance abuse relapses: CLO (25%) < Other (37.5%) p=0.05	

Swanson et al [34]	Prospective observational study. Study duration: 3 years Aims: to examine the influence of medication class and compliance on substance use Evaluation instruments: AUS, DUS; SCAP-HQ	362 patients with SCZ-S Comorbid diagnosis: Current SUD N=87 (24.1%)	3 groups: AAPs (CLO, RIS, OLA) TPAs No APs		Unspecified	Outcome: reducing substance use Study completion: - one-year follow up: 80.4% - two-year follow up: 70.7% - three-year follow up: 47.5% Results: Factor associated with a reduced substance use: - AAPs compliant use, with respect to no medication (OR=0.55, p<0.01) and TAPs (OR = 0.50, p < 0.05). Factor associated with an increased substance use: - Psychotic symptoms (OR = 1.19, p < 0.05).	Three-year attrition rate: 56.6%
Zimmet et al [35]	Retrospective study Evaluation period: 6 years Aim: to investigate the efficacy of CLO on psychiatric symptoms and substance use Evaluation instruments: Charts, Structured interviews	58 patients with a SCZ (N=32) or SCA (N=19) Males: 72.4% Age range: 27-59 years Mean age: 41.4 years Comorbid diagnosis: Current SUD N=36 (62.1%) Lifetime SUD N= 58 (100%)	CLO current treatment group (N=43, median length of treatment: 3.29 years) CLO former treatment group (N=15, median length of treatment: 0.56 years)		Alcohol only N=26 (44.8%) Cannabis only N=4 (6.9%) Polyabuse N=28 (48.3%)	Outcomes: - reduction of substance use - reduction of psychiatric symptoms CLO current treatment group (N=43) results: - Current SUD (N=28). Significant reduction of substance use: 85% Significant correlation between symptoms reduction and all substance use (Rs=0.55, p=0.002) - Lifetime SUD (N=15): 0% relapsed in substance use CLO former treatment group (N=15) results: - Current SUD (N=8): Significant reduction of substance use: 88% Significant reduction of psychotic symptoms: 75% - Lifetime SUD (N=7): 0% relapsed in substance use	Dropouts N=15, (25.9%) due to: - refusal of treatment - increased myoglobin - sedation - delusions about obtaining blood samples - ongoing alcohol abuse

Green et al [36]	Retrospective study Evaluation period: 1 year Aims: to compare CLO to RIS in terms of substance abstinence rates Evaluation instruments: Charts	41 Outpatients with SCZ (N=30) or SCA (N=11) Males: 75.6% Mean age: 48.7 years Comorbid diagnosis: SUD N=41 (100%)	RIS group N=8 mean dose: 9.9 mg/day CLO group N=33 mean dose: 439.6 mg/day		Alcohol only N=20 (48.8%) Cannabis only N=9 (21.9%) Alcohol + cannabis N= 12 (29.3%)	Outcome: substance cessation 1-year follow up results complete data available for 32 patients (78%): (RIS N=8, CLO N=24) Abstinence rates: RIS N=1 (12%), CLO N=13 (54%) Chi squared p=0.05	
Petrakis et al [37]	Retrospective study Evaluation period: 1 year Aims: to compare AAPs to TAPs in terms of substance use Evaluation instruments: Veteran Affairs Healthcare System workload databases, ASI	249 outpatients affected by SCZ, SCP, SCA. Mean age: 46.4 years Males: N= 238 95.6%. Comorbid diagnosis: SUD N=249 Dysthymia N=74 (29.7%) PTSD N=50 (20.1%) Major depression/ bipolar N=110 (44.2%) Other psychosis N= 59 (23.7%)	At baseline: TAPs (N=79) AAPs (N=170): - OLA N=86 - QUI N=8 - RIS N=76 At follow up: TAPs (N=55) AAPs (N=198): - OLA N=110 - QUI N=12 - RIS N=69 - CLO N=3 Study groups: - maintained on AAPs (N=161) - switched to AAPs (N=33) - treated with TAPs (N=55)		Alcohol: N=204 (81.9%) Substances (unspecified) N= 217 (87.1%)	Outcome: reduction of ASI scores Paired t tests results: - the group as a whole showed a significant reduction of 5 ASI scores over time: alcohol use (p=0.012), drug use (p=0.032), psychological (p<0.001), medical (p=0.025), family (p=0.001) - maintained on AAPs showed a significant reduction of 4 ASI scores: alcohol use (p=0.010), drug use (p=0.018), psychological (p=0.007), family (p=0.007) - switched to AAPs showed a significant reduction of 3 ASI scores: psychological (p=0.002), family (p=0.045), employment (p=0.023) Multiple regression Analysis results: - no significantly greater improvement in any ASI scores for maintained on AAPs (p>0.10) or switched to AAPs (p>0.30) with respect to TAPs	

Abbreviations: SCZ: Schizophrenia; SCP: Schizophreniform disorder; SCA: Schizoaffective Disorder; SCZ-S: Schizophrenia Spectrum Disorder; SUD: Substance Use Disorder; AAPs: Atypical Antipsychotics; TAPs: Typical Antipsychotics; CPZ: Clorphromazine; CLO: Clozapine; FLU: Fluphenazine; HAL: Haloperidol; OLA; Olanzapine; RIS: Risperidone; QUI: Quietapine; ZUC: Zuclopenthixol; A.I.M.S: Abnormal Involuntary Movement Scale; ASI: Addiction Severity Index; AUS: Alcohol Use Scale; BAS: Barnes Akathisia Scale; BMI: Body Mass Index; BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impressions; DDQ: Drug Desire Questionnaire; DUS: Drug Use Scale; ESRS: Extrapyramidal Symptom Rating Scale; HRSD: Hamilton Rating Scale for Depression; MADRS: Montgomery-Asberg Depression Rating Scale; OCDUS: Obsessive–Compulsive Drug Use Scale; PANSS: Positive And Negative Schizophrenic Symptoms; SADS-C+PD: Schedule for Affective

Disorders and Schizophrenia, Change Version with psychosis and disorganization items; SAMM: substance abuse management model; SANS: Scale for Assessment of Negative Symptoms; SAS: Simpson Angus Scale; SATS: Substance Abuse Treatment Scale; SCAP-HQ: Schizophrenia Care and Assessment Program Health Questionnaire; SCID-IV: Structured Clinical Interview for DSM-IV; SWN: Subjective Well-Being under Neuroleptics scale; UKU: Udvaig for kliniske Side Effects Rating Scale; VCCQ: Voris Cocaine Craving Questionnaire

A 6-week multicentre RCT by Van Nimwegen et al [29] enrolled 128 outpatients with schizophrenia, schizophreniform or schizoaffective disorder, 41 (32%) of them reporting a current cannabis abuse disorder. The aim of the study was to test the efficacy of OLA (mean dosage 11.1 mg/day) or Risperidone (RIS) (mean dosage 3 mg/day) on subjective wellbeing and cannabis craving. The OLA group was composed of 63 patients, 20 of which with comorbid SUD, and the RIS group of 65 patients, 21 of which with comorbid SUD. At the end of the study, the authors did not found any between-treatment effect in terms of craving and number of joints. Both drugs were equally efficacious in improving subjective wellbeing. The percentage of dropouts was slightly higher in the OLA group (31.4%) with respect to the RIS group (16.4%).

In 2011 Sevy et al [30] published the results of a 16-week RCT involving 49 patients with first-episode psychosis (SCZ, SCP, SCA) and comorbid lifetime cannabis use disorder. Many patients reported other substances abuse, especially alcohol (N=19, 38.7%) and cocaine (N=5, 10.2%). The participants were randomly assigned to receive OLA (N=28) or RIS (N=21). At the end of the study, both treatments were equally efficacious in reducing positive symptoms, asociality-anhedonia and current cannabis use. A significant increase over time in weight and Body Mass Index (BMI) was observed in both groups.

In 2002 Smelson and colleagues [31] conducted a 6-week OLT comparing RIS to typical neuroleptics in the treatment of schizophrenic patients with co-occuring cocaine dependence. Eighteen patients treated with TAPs (HAL, fluphenazine, chlorpromazine) were assigned to receive RIS (N=8) or to continue their previous treatment (N=10). At study completion, patients in the RIS group showed a significantly reduced cocaine craving ($p<0.01$) and a lower rate of substance use relapses with respect to TAPs group (12.5% versus 70%, p=0.025). A trend versus a greater reduction in PANSS global (p=0.079) and negative (p=0.068) scores was also observed in the RIS group. With regard to dropout rate, it was lower in the RIS group (25% versus 70%) but the difference did not reach the statistical significance (p=0.15).

Rubio et al. [32] carried on a large 24-week OLT in 2006, involving 115 schizophrenic subjects with substance abuse, mainly alcohol (87.8%), cannabinoids (71.3%) and cocaine (26.1%). Fifty-seven patients were assigned to long-acting injectable Risperidone (RIS) and 58 to long-acting injectable zuclopenthixol (ZUC). The study completion was very high (92.2%), with no significant between-group differences. After 24 weeks of treatment, all the patients (100%) relapsed in the substance abuse, but during the study period the subjects treated with RIS showed a lower number of positive urine tests and a better compliance to the substance abuse management model (SAMM) with respect to those treated with ZUC. Moreover, RIS appeared more efficacious than ZUC in reducing PANSS global, total and negative scores, even though the number of psychiatric hospitalizations during the study period was similar in the two treatment arms (RIS: 17.5%, ZUC: 18.9%). The tolerability profile was better for RIS, with less subjects requiring anticholinergic medication (27% versus 48.5%, respectively) and lower scores at the Extrapyramidal Symptom Rating Scale (ESRS) [44] and the Udvaig for Kliniske (UKU) Side Effects Rating Scale [45], compared to ZUC.

As a part of a 10-year prospective observational study on dual-diagnosed patients (N= 233), Brunette and colleagues [33] published the results of a 2-year follow up limited to SCZ or SCA patients treated with antipsychotic medications, who experienced a 6-month SUD remission (N=95). The aim of the study was to compare Clozapine (CLO) to other medications (both TAPs and AAPs) in preventing substance abuse relapses. The most common abused substances were alcohol, cannabinoids and cocaine. At baseline, patients were treated with CLO (N=25), RIS (N=4), OLA (N=4) and TAPs (N=62). At one-year follow up, the number of substance abuse relapses was significantly lower in the CLO group, with respect to the other treatments group (8% versus 40%, respectively, p=0.003). Moreover, CLO was better than other treatments in ameliorating Alcohol Use Scale (AUS), Drug Use Scale (DUS) and Substance Abuse Treatment Scale (SATS) [46] scores ($p<0.05$). At two-year follow up (data available from 64 patients, 67.4%) the superiority of CLO with respect to other treatments in preventing substance use relapses was confirmed (25% relapses versus 37.5%, respectively, p=0.05).

A 3-year prospective observational study was conducted by Swanson et al [34], aiming at clarifying the influence of medication class and compliance on substance use outcomes in 362 patient with SCZ-S, 87 (24%) of which with comorbid SUD. Based on their pharmacological treatments, patients were divided into 3 different groups: AAPs (CLO, RIS, OLA), TAPs and APs free. After 3 years, the cumulative attrition rate was 56.7% and did not significantly differ in patients with and without SUD at baseline. The authors reported a significant association between substance use and severity of psychotic symptoms ($OR = 1.19$, $p < 0.05$), as assessed by the Schizophrenia Care and Assessment Program Health Questionnaire (SCAP-HQ). A AAPs compliant treatment was associated to a reduced substance use during the study, with respect to no medication ($OR=0.55$, $p<0.01$) or TAPs treatment ($OR = 0.50$, $p < 0.05$).

In a 6-year retrospective survey conducted by Zimmet et al [35], 58 SCZ or SCA patients currently (N=43, median length of treatment 3.29 years) or previously treated (N=15, median length of treatment 0.56 years) with CLO and affected by a comorbid lifetime SUD (alcohol N=26, 44.8%; cannabis N=4, 6.9%, polysubstance abuse N=28, 44.3%) were enrolled to test the efficacy of CLO in reducing both substance use and psychotic symptoms. A current SUD, at the beginning of CLO treatment, was observed in 36 subjects (N=62.1%). In the group currently treated with CLO, a significant reduction (about 85%) in substance use was observed among the 28 active substance users. Moreover, a significant correlation was observed among reduced substance use and decreased psychotic symptoms (Rs=0.55, p=0.002). None of the 15 non-active substance users (0%) relapsed. In the group formerly treated with CLO (N=15), the majority of the subjects with a current SUD (N=8) experienced a significant reduction of substance use (N=7, 87.5%) and psychotic symptoms (N=6, 75%), and none of those with a past SUD relapsed (0%).

Green et al [36] published a 1-year retrospective study in 2003, evaluating the effects of CLO and RIS on substance use in SCZ /SCA patients with comorbid SUD. Only patients with at least one-year of AAP treatment were included in the study (N=41): 8 were treated with RIS and 33 with CLO. The substances abused were alcohol (48.8%), cannabis (9.4%) or both (29.3%). The study outcome was the cessation of substance use. At 1-year follow up, complete data were available for 32 patients: 8 patients in the RIS group and 24 patients in the CLO group. The abstinence rate was significantly higher in the CLO group with respect to the RIS group (54% versus 12%, p=0.05).

A large 1-year retrospective survey was carried out by Petrakis et al [37] on 249 SCZ-S patients with concomitant SUD (alcohol abuse N= 204, 81.9%; drug abuse N= 217, 87.1%), to compare the efficacy of AAPs and TAPs on substance use. Patients were divided into 3 groups: maintained on AAPs during the study period (N=161), switched to AAPs (N=33) or treated with TAPs (N=55). The AAPs administered at follow up were OLA (N=110, 34.2%), RIS (N=69, 27.7%) QUI (N=12, 4.8%) and CLO (N=3, 1.2%).

At the end of the study, paired t-tests showed a significant reduction of several Addiction Severity Index (ASI) [47] subscales over time in the whole sample and in the patients maintained on or switched to AAPs. On the other hand, multiple regression analysis failed to find any significant between-group differences.

Discussion

Substances-related issues are extremely frequent in schizophrenic patients. The impact of SUD on the course of the psychiatric illness is dramatic, increasing the number of hospitalizations [48] and reducing the adherence to pharmacological and rehabilitation treatments [49].

Nevertheless, dual-diagnosed subjects are usually excluded from pharmacological trials to avoid confounding effects and high rate of dropouts. As a consequence, there are few available data on this particular clinical population and it is difficult to obtain clear guidelines. In fact, with respect to the large amount of data on schizophrenic patients without SUD, we could individuate only 12 studies reporting the efficacy of AAPs on dual-diagnosed patients.

As reported in previous studies [3,22,50], we observed that the majority of the enrolled patients were males (the percentage varied from 70.5% to 100% in the ten studies that reported gender distribution), and relatively young (mean age range: 25-49 years). In the general population, the rates of drug abuse are 2-3 times higher in men than in women, and a different impact of male/female sexual hormones on the brain reward system has been proposed to explain these differences [51].

For what regard schizophrenia, an increased incidence in males (male/female ratio: 1.4) was also found [52] and the role of illicit drugs as risk factors and of estrogens as protective factors in the development of schizophrenia were suggested [53]. Dual-diagnosed schizophrenic patients are usually males and younger than those without comorbid SUD, thus supporting the hypothesis that drug abuse, especially cannabis, may accelerate the onset of psychosis in those subjects at augmented genetic/endocrine risk for psychosis[54].

The substances of abuse/dependence were specified in ten studies, the most represented being alcohol (N=436), cannabis (N=271) and cocaine (N=137). Other substances, such as opiates (N=14), hallucinogens (N=15) and amphetamines (N=5), were rare.

In ten studies the number of subjects treated with each AAPs was reported: olanzapine (N=364), risperidone (N=232), clozapine (N=119) and quietapine (N=12). None of the selected studies used placebo as a comparator. AAPs were compared to TAPs in eight studies, and to other AAPs in three studies [29,30,33]. Only in the study by Zimmet et al [35], a single AAP (clozapine) was tested without any comparison group. The study completion was quite high in both clinical trials (from 50% to 92.2%) and observational studies (from 47.5% to 100%).

When comparing the efficacy on substances-related problems, AAPs resulted more efficacious than TAPs in 4 studies (one RCT, two OLTs and one prospective study) [28,31,32,34] equally efficacious in two studies (one RCT and one retrospective study) [10,37] and less efficacious in one RCT [27]. A similar efficacy of AAPs and TAPs was observed on psychotic symptoms.

In those studies comparing different AAPs, no significant differences emerged between risperidone and olanzapine in two RCTs [29,30], whereas clozapine resulted more efficacious than other AAPs in two observational studies [33,36]. In the retrospective study by Zimmet et al [35], clozapine was the only tested medication and a good efficacy in reducing both psychotic symptoms and drug use was highlighted. Even though not supported by RCTs, a superiority of clozapine with respect to other AAPs in dual-diagnosed schizophrenic patients have been previously suggested, and explained by a positive effect on the disrupted dopamine-mediated brain reward circuit throughout its multiple actions on neurotransmitter systems [55].

In terms of safety, all the revised studies reported the number of dropouts, but only five of them indicated the observed side effects [27,29,30,32,35]. With respect to TAPs, less (but not absent) extrapyramidal symptoms were reported during AAPs treatment, thus confirming the results of a recent review comparing first- to second-generation drugs in psychiatric populations [56]. The most reported side effects related to AAPs were weight gain and sedation. In a meta-analysis comparing efficacy and tolerability of 15 antipsychotics in the treatment of schizophrenia, Leucht and co-authors [57] analysed the results of 212 clinical trials, involving more than 43000 subjects, and reported that antipsychotics significantly differed from one another for both side effects and efficacy. In terms of efficacy, clozapine was the best option, with olanzapine and risperidone reaching the third and fourth place respectively. When evaluating the tolerability profile, clozapine and olanzapine were associated to an augmented risk of weight gain and sedation, whereas a higher rate of increased prolactin level was observed in patients treated with risperidone. In dual-diagnosed schizophrenic patients, great attention should be paid to comorbid medical conditions frequently observed in this clinical population (i.e: hepatic, infectious or cardiac disease) that may increase the toxicity of psychopharmacological treatments.

Limits of the Analyzed Studies

The results of the reviewed studies should take into account their methodological limitations, such as the lack of placebo arms, the small sample sizes (less than 50 patients in five of the twelve studies included in the qualitative synthesis) and the limited drug

screen procedures. Moreover, the effects of drug use were not always exhaustively analyzed: some studies focused only on the acute effects of substance intake, other on the residual long-term consequences of drug addiction and only a few of them clearly reported the observed side effects. As another limit, the influence of important clinical variables, such as the duration of the illness and the onset of SUD (prior or after the schizophrenia onset) was seldom considered in the statistical analysis.

Conclusion

Our review suggests that some AAPs, namely clozapine, olanzapine and risperidone, may be a promising therapeutic option in schizophrenic patients with comorbid SUD, with a favorable efficacy/safety profile. Nevertheless, our results should be interpreted with caution due to the few available data and significant study limitations.

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