

# Pharmacological treatment for dual diagnosis: a literature update and a proposal of intervention

## *Quali strategie farmacologiche per la doppia diagnosi in alcologia? Criticità e prospettive di intervento*

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**SUMMARY. Background.** It has long been appreciated that alcohol use disorder (AUD) is associated with increased risk of psychiatric disorder. As well, people with history of mental disorder are more likely to develop lifetime AUD. Nevertheless, the treatment of dual diagnosis (DD) in alcohol addiction still remains a challenge. The efficacy of pharmacological treatment for these patients has been widely investigated with controversial results. Patients with untreated psychiatric disorder are at higher risk to return to drinking and tend to do so more quickly. The aim of this review was to collect clinical data for developing guidelines for the pharmacological treatment of psychiatric diseases in a population with AUD. **Materials and methods.** A literature review was conducted using the following databases: PubMed-NCBI, Cochrane database, Embase Web of Science, and Scopus, including studies published between 1980 and 2015. Search terms were: “guideline”, “treatment”, “comorbidity”, “substance abuse”, “alcohol”, “dual-diagnosis”, “antidepressant”, “antipsychotic”, “mood-stabilizer”. Out of 1521 titles, 84 studies were included for their relevance on pharmacological treatment of psychiatric disorders in people with AUD. **Results.** Different drugs were collected in major pharmacological classes (antidepressant, mood-stabilizer, antipsychotic), in order to identify their proved efficacy for treating specific psychiatric disorder in the AUD population. Data were selected and verified for publications from randomized clinical trials, open-label trials and case reports. **Conclusions.** DD in alcohol dependence is a complex clinical entity, and its high prevalence is supported by epidemiological data. Pharmacological management of psychiatric disorders in patients with AUD remains partially anecdotal. Based on reviewed articles, we propose a classification of psychiatric medications for treatment of mental disorders comorbid with AUD, listed with evidence-based recommendations. More research is needed to obtain and collect clinical data, in order to organize and share evidence-based guidelines.

**KEY WORDS:** alcohol use disorder, treatment, guideline, evidence-based, dual diagnosis, antidepressant, antipsychotic, mood stabilizer.

**RIASSUNTO. Background.** Nonostante la rilevanza clinica ed epidemiologica della compresenza di disturbi psichiatrici nella popolazione di pazienti con disturbo da abuso di alcol (DUA), c'è un'importante lacuna nella definizione di metodi e strategie di intervento farmacologiche condivise. Tra le molteplici proposte terapeutiche, non esiste un modello che si sia rivelato valido ed efficace per la gestione farmacologica della doppia diagnosi (DD) in ambito alcologico. Il trattamento non ottimale del disturbo mentale in comorbilità con DUA può portare a un aumento nel rischio di ricadute, e in pazienti che avessero un DUA in comorbilità. Lo scopo di questa rassegna è fornire dati clinici per stilare linee-guida specifiche per la terapia dei disturbi psichiatrici in pazienti con DUA, ad integrazione e completamento di quelle già esistenti. **Materiali e metodi.** La rassegna è stata effettuata utilizzando le seguenti banche dati: PubMed-NCBI, Cochrane database, Embase, Web of Science e Scopus, prendendo in considerazione articoli pubblicati dal 1980, anno di pubblicazione del DSM III, al 2015. Le ricerche sono state condotte incrociando le seguenti parole chiave: “guideline”, “treatment”, “comorbidity”, “substance abuse”, “alcohol”, “dual-diagnosis”, “antidepressant”, “antipsychotic”, “mood-stabilizer”. Altri articoli sono stati desunti dalla bibliografia presente in articoli già selezionati. Dei 1521 articoli emersi, 84 sono stati inclusi in questo lavoro per la loro rilevanza sulla terapia farmacologica dei disturbi psichiatrici in pazienti con DUA. **Risultati.** Sono stati presi in considerazione articoli in cui un farmaco è stato prescritto *in-label*, ossia nella terapia di un disturbo per cui ha indicazione in scheda tecnica, e in pazienti che avessero un DUA in comorbilità. Le molecole incluse nella rassegna appartengono alle principali classi di farmaci utilizzati nella pratica psichiatrica (antidepressivi, anticonvulsivanti/stabilizzatori del tono dell'umore, antipsicotici). **Conclusioni.** La DD in campo alcologico è un'entità clinica complessa e di difficile definizione, ma con un impatto epidemiologico certo. La gestione farmacologica dei disturbi psichiatrici in pazienti con DUA dovrebbe essere orientata da linee-guida specifiche, fondate su evidenze di letteratura. Sulla base dei risultati della presente rassegna viene proposta una classificazione dei farmaci utilizzati nella terapia dei disturbi psichiatrici in comorbilità con DUA, ordinati secondo differenti gradi di raccomandazione a seconda delle evidenze presenti in letteratura. Ulteriori ricerche potrebbero contribuire a trattare un profilo di intervento farmacologico specifico per i pazienti con DD alcol-correlata.

**PAROLE CHIAVE:** dipendenza da alcol, trattamento, linee-guida, evidence-based, doppia diagnosi, stabilizzatori dell'umore, antidepressivi, antipsicotici.

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### INTRODUCTION

The interaction between psychoactive substance use and psychopathological disorders is a complex clinical phenomenon characterized by important limits, which always posed critical challenges both as diagnostic/nosographic level and in terms of treatment strategies, particularly for pharmacological strategies. The term “dual diagnosis” (DD), introduced by the World Health Organization in 1995, is used to indicate the concomitance of a substance use disorder and another psychiatric disorder<sup>1</sup>. It is hard to identify the etiopathogenetic causality because often the two conditions affect each other, making each clinical situation, with specific features and specific treatment needs. In fact, the substance use disorder often complicates the psychopathological clinical status, makes it more heterogeneous, difficult to frame and therefore difficult to treat even with specific pharmacological interventions<sup>2</sup>. Patients with DD are also considered “difficult patients” because of a tendency to poor compliance with therapies, high drop-out rates, high hospitalization rates, and often organ damage making very hard the pharmacological management<sup>3</sup>. In a previous work we have taken into account the complexity of the nosographic debate about DD<sup>4</sup>. At this point, it seems appropriate to recall the interesting novelties proposed by the 5th Edition Diagnostic and Statistical Manual of 2013 (DSM-5)<sup>5</sup>. «In DSM-5 the new substance use disorder diagnosis can be considered of dimensional type: abuse and addiction distinct diagnosis are combined into a single spectrum of 11 symptoms and according to their number, a greater or lower severity is assigned. In addition, “craving” is present as a nosographic criterion: for the first time, the quality of the patient’s subjective experience becomes a diagnostic criterion, also thanks to the important studies conducted in this field, starting with Anton’s contributions in the early 1990s».

Additionally, the DSM-5, more distinctly than in the past, discusses of substance-induced or substance-independent mental disorder. Alcohol-induced disorders typically develop in close connection with intoxication/withdrawal from alcohol and improve with the withdrawal, even without a specific treatment or therapy. Alcohol-independent disorders, however, generally occur prior to the onset of the alcohol use disorder (AUD) and require a specific therapeutic approach. In this case we can properly talk of a DD.

Essentially, DSM-5 more operationally detailing the dependent-independent concept allows to completely overcome the old and often “paralyzing” primary-secondary dichotomy by asserting that, if:

- psychopathological disorder exhibits clinical relevance (i.e., meets DSM-5 criteria) for a longer period than one month after substance withdrawal (with the exception of possible persistent disorders such as neurocognitive disorders);
- there is a clinical history indicating an occurrence of psychopathological disorder prior to substance intoxication/abuse.

We are in front of a psychopathological disorder that is independent by substance use and, as such, it should be readily addressed and managed both from a pharmacological and psychotherapeutic point of view, based on the patient’s general clinical picture<sup>4</sup>.

In addition to the complex nosographic framing, DD is a phenomenon of epidemiological relevance, as reported by various literature studies. It has been observed that approximately 50% of people with AUD have had at least one concomitant psychiatric disorder in their lifetime. In particular, mood disorders, unipolar and bipolar disorders, anxiety disorders and personality disorders belonging to B and C clusters prevail<sup>6</sup>. Despite the clinical complexity and the critical epidemiological impact of DD in alcoholology, the pharmacological treatment in these situations is poorly defined and worth of deepening. To date, no shared guidelines have been identified in order to guide and standardize pharmacological intervention strategies: the main contributions presented in the literature are as follows.

### DUAL DIAGNOSIS: GUIDELINES IN THE LITERATURE

In Deruvo et al.<sup>7</sup> publication, DD and its treatment difficulties have been widely discussed. The authors’ work focused on previous studies testing the possible use of some psychiatric drugs. In a considerable part of these studies, a psychiatric drug was administered to patients with AUD without psychiatric comorbidity, with the purpose to treat the abuse and/or addiction, such as craving or acute abstinence symptoms. In this regard, studies in which is speculated the tricyclic antidepressants use<sup>8</sup> for addiction treatment are cited, or the selective serotonin reuptake inhibitors (SSRIs) as promising options, for their effectiveness in reducing the craving for alcohol. A Rossinfonte’s study<sup>9</sup> asserts that SSRIs in alcoholism treatment do not act as antidepressants, but have a specific effect on addiction, reducing craving and relapse frequency. Moreover, carbamazepine seems to be a possible therapeutic option in mild or moderate alcoholic withdrawal management, showing more efficacy of benzodiazepines even in reducing relapse risks. In a study of 16 patients<sup>10</sup>, valproic acid was also used in withdrawal based therapy compared with benzodiazepines<sup>11</sup>. Both molecules, however, seems to be contraindicated in case of liver disorders, which are quite common in AUD patients. Generally, Deruvo et al.<sup>7</sup> suggest that if the drug shows evidence of efficacy for both the AUD and the psychiatric disorder (occurring separately), it is possible that this drug may be useful in DD patient’s treatment when these or more disorders coexist. It is a shared opinion that this logic connection should be corroborated by further specific clinical trial in DD patients. The Brazilian Association of Studies on Alcohol and Other Drugs (ABEAD) guidelines, underline the importance of a restrictive benzodiazepine use in DD patients due to cross-addiction risks with alcohol<sup>12</sup>. Instead, buspirone showed greater safety profile. However, it is underlined the low availability of controlled studies examining specific populations of patients with psychiatric disorders in comorbidity with AUD. The Queensland Health Dual Diagnosis Clinical Guidelines provide a picture of commonly psychiatric medication classes used and provide general use information together with practical advice<sup>13</sup>. Particular attention is paid to the possible interaction between the used drug and the substance of abuse (alcohol in this case), as well as the abuse potential of the psychiatric drug itself. It is also reported the importance to assess the presence of alcohol-related organic

pathologies, given the poor tolerability of some psychiatric drugs. Compared to antidepressant medication, it is recommended to monitor the possible occurrence of serotonergic activation symptoms, especially during the alcohol detoxification phase, and the importance of a careful differential diagnosis with any symptoms of alcohol addiction syndrome. Even in this case, no comprehensive guidance is given about the use of specific drugs for patients with drug related DD.

CANMAT (Canadian Network for Mood and Anxiety Treatments) guidelines provide a guidance on pharmacological therapy in DD, including studies in patients with substance abuse and psychiatric comorbidity<sup>14</sup>. For example, in bipolar patients with AUD, a good mood-effect, using quetiapine in addition with first level options for bipolar disorder, is reported. Preliminary observations suggest the usefulness of topiramate and gabapentin in bipolar subjects with AUD, whereas lithium does not appear to be a very useful option, given lower response rates and the reduced tolerability. Among antidepressants, mirtazapine should be preferred to tricyclic antidepressants for its better tolerability and the same efficacy. In this interesting literature review, various types of substance use disorders (including AUD) are considered, and has been reviewed the evidence about the comorbidity only with mood disorders. The main goal of our work is to provide an overview of clinical available trials in the literature in DD (AUD) samples to suggest, according to the evidences, useful pharmacological strategies. These options can be the basis to build evidence-based treatment algorithms. In the choice of articles, only those in which the drug has been tested in-label, were considered. In the Results section will be analytically described the found trials, and according to these ones it will be proposed a recommendation for each tested drug in the Discussion section.

**MATERIALS AND METHODS**

A review was made using the major international databases: PubMed-NCBI, Cochrane database, Embase Web of Science, and Scopus. Published articles from 1980, the year of publication of DSM-III, until 2015, were considered. The search keywords were: “guideline”, “treatment”, “comorbidity”, “substance abuse”, “alcohol”, “dual-diagnosis”, “antidepressant”, “antipsychotic”, “mood-stabilizer”. Other articles have been selected from the references of previously selected articles. Of 1521 emerged works, 84 were included in this paper for their relevance in pharmacological therapy of psychiatric disorders in AUD patients.

**RESULTS**

There is no specific literature review on medication therapy management in AUD patients with comorbid different psychiatric disorders. International guidelines do not seem exhaustive and in agreement to suggest a clear diagnostic iter and treatment strategies. The results of our review are analytically described below, and classified in specific pharmacological classes.

**Antidepressants**

Among the various AUD comorbid disorders, mood disorders are one of the most represented clinical disorder<sup>15</sup>.

Several studies show a high comorbidity rate between AUD and mood disorders. The Epidemiological Catchment Area (ECA) study results show the presence of affective disorders in 13.4% of subjects diagnosed with AUD (compared with a prevalence of 7.5% in the general population) and AUD diagnosis in 21.8% of patients with mood disorder<sup>16</sup>. Grant and Harford<sup>17</sup> assessed the comorbidity between alcohol dependence and major depression in a 42,800 adult people sample, detecting a DD in 32.5% of subjects and only in 11.2% an AUD diagnosis without major depression.

Finally, in a sample of approximately 8,000 subjects aged from 15 to 64 years, 28.1% of them met the mood disorder and alcohol dependence criteria<sup>18</sup>. Concerning the pharmacotherapy of comorbid depressive disorders with AUD, contrasting data are available in the literature. As general indications, some studies have suggested the usefulness to start the antidepressant therapy already in the detoxification phase. Brady and Roberts<sup>8</sup> are not of this opinion, recommending to not set pharmacological treatment at this stage to not mix the activation therapy signs with the possible acute alcohol abstinence symptoms (anxiety, agitation, hyperactivity of the nervous system). The indication to formulate a depressive disorder diagnosis not less than 2-4 weeks after the last intake, is also reiterated. Table 1 shows the available data for a single antidepressant use in patients with anxiety-depressive spectrum and AUD. In a number of randomized trials<sup>19,20</sup>, the escitalopram effectiveness has been shown to reduce depression symptoms in more than 50% of AUD patients. In particular, the drug appears to be more effective in subjects with late-onset depression (>30 years)<sup>21</sup>. A controlled study compared the effectiveness of escitalopram monotherapy, compared with escitalopram/acamprosate (a drug used to reduce alcohol craving). In the group treated with the associated therapy, marked improvements in depressive symptoms and a reduced weekly and monthly alcohol consumption were observed. The sample exiguity did not allow to detect statistical

Table 1. Antidepressive drugs and levels of recommendations.

Drug	Disease	Evidence
Paroxetine	Anxiety disorders	B1
Sertraline	Depressive disorders	B2
Escitalopram	Depressive disorders	B1
Fluoxetine	Depressive disorders	B2
Fluvoxamine	Depressive disorders	B2
*Trazodone	Insomnia	B2
Venlafaxine	Depressive disorders	B2
Mirtazapine	Depressive disorders	B2
Mirtazapine	Anxiety disorders	B2
Desipramine	Depressive disorders	B2
Imipramine	Depressive disorders	B2

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significance<sup>22</sup>. Conversely, a recent controlled study on patients with depression and AUD did not show any significant differences neither in affective symptoms nor in alcohol consumption between patients treated with citalopram or placebo<sup>23</sup>. Sertraline, in combination with cognitive-behavioral therapy, has been shown to be helpful in reducing both depressive symptoms and daily alcohol consumption<sup>24</sup>. In a double-blind study of 14 weeks, a total of 170 patients were treated with sertraline, naltrexone (anti-craving drug), or with sertraline/naltrexone. Patients treated with associated therapy reported higher alcohol abstinence rates and maintained it for several days before a possible relapse, as well as a pronounced depressive symptom reduction<sup>25</sup>. In three different studies, the effectiveness of fluoxetine in adolescents with AUD and major depression was tested at short and long term. In the acute phase, the drug, administered for 12 weeks, has been shown to be effective both on depressive symptoms and to reduce the severity of alcohol consumption. At 3 and 5 years of follow-up, although the symptomatic severity was still reduced, the relapse index was important (about 50%)<sup>26-28</sup>. Among the dual-action antidepressant drugs, one of the most tested drug is mirtazapine. The amitriptyline and mirtazapine effectiveness was compared, showing response rates for depressive symptoms and comparable reduced craving, but a better tolerability for mirtazapine<sup>29</sup>. In an open-label, multicenter study of 143 patients, an 8-week treatment with mirtazapine resulted in a significant improvement in depressive and anxiety symptoms, as well as in a reduction in craving and alcohol compulsiveness (measured with Obsessive-Compulsive Drinking Scales)<sup>30,31</sup>. These data were confirmed by a study published in 2012 that reported good mirtazapine response rates associated with a marked reduction in weekly alcohol consumption (34 to 13 alcoholic units per week)<sup>32</sup>; 75% of subjects also found a job during the treatment period. In the same patient group, re-evaluated after 2-year follow-up, similar results were reported, indicating a stable response time<sup>33</sup>. Venlafaxine also showed to be effective in depressive symptoms, in parallel with a significant reduction in severity of dependence<sup>34</sup> measured by the European version of the Addiction Severity Index<sup>35</sup>. Patients treated with escitalopram and aripiprazole reported an improvement in depressive symptoms and a reduction in craving compared to escitalopram treatment alone<sup>36</sup>. The escitalopram/reboxetine combination showed also to be effective to reduce depressive symptoms and the severity of dependence<sup>37</sup>. In addition to depressive disorders, most of the new generation antidepressant drugs are also indicated for several anxiety disorders. The ECA study reports that around 20% of patients with AUD have comorbid anxiety disorder, and 18% of subjects with anxiety disorder show alcohol addiction or abuse symptoms<sup>16</sup>. The National Comorbidity Survey reported a prevalence of 23% for anxiety disorders in men with lifetime alcohol abuse and of 49% in women. Conversely, in subjects diagnosed with AUD, anxiety disorders are present in 36% of men and 61% of women<sup>38</sup>. Among anxiety disorders, panic disorder and social anxiety disorder are quite common in subjects with AUD. It has been estimated that every 5 patients arriving at clinical observation for social anxiety, one suffers of AUD<sup>39</sup>. Paroxetine is the drug with more evidences in these patients. In three different studies, an improvement in the social anxiety symptomatology has been reported, with a reduction in alcohol consumption associated with social exposure (drinking-to-

cope)<sup>35,40,41</sup>. In particular, the authors suggest that drug therapy, reducing social contact anxiety levels, helps patients to face with emotionally high-impact situations without automatically recurring to alcohol as self-medication. To measure this effect, the authors developed and validated a Social Anxiety Drinking Scale<sup>42</sup>. Moreover, mirtazapine showed to be effective to reduce social anxiety symptoms, in a sample of 33 subjects undergoing an alcohol detoxification program<sup>43</sup>. A recent controlled trial investigated the venlafaxine effectiveness, in association with a cognitive-behavioral therapy (CBT), in a sample of anxious patients with AUD. Pharmacologically-treated patients did not show any significant improvement compared to patients who did CBT alone<sup>44</sup>. A neurophysiological study conducted on 16 AUD patients with sleep disorders reported an improvement in sleep efficiency in subjects treated with trazodone compared to placebo<sup>45</sup>. In several studies, the effectiveness of sertraline in AUD and post-traumatic stress disorder (PTSD) patients has been demonstrated. Specifically, in a 94 patients performed randomized controlled trial (RCT), subjects with early onset PTSD and dependence showed better response rates in terms of post-traumatic symptom reduction and daily alcohol consumption compared to patients with late onset PTSD and more serious addiction<sup>46</sup>. A recent randomized study confirmed these findings, showing a better response for both disorders in the sertraline-treated group in association with cognitive-behavioral intervention compared with the CBT-only group<sup>47</sup>. A study conducted in 88 American Army veterans with PTSD and alcohol dependence, compared the effectiveness of paroxetine and desipramine monotherapy or associated with naltrexone<sup>48</sup>. The group treated with desipramine reported more incisive results in terms of alcohol intake reduction, while the combination with naltrexone improved the effectiveness of both drugs on craving. In each of four treatment groups, improvements in post-traumatic and depressive symptoms were noted, with no significant differences.

#### **Anticonvulsants/mood stabilizers**

Anticonvulsants have been long used in psychiatric practice, so much so that they were indicated for various psychopathological disorders treatment. In particular, the majority of them is used as mood stabilizers in bipolar spectrum disorders treatment. The relationship between alcohol dependence and bipolar disorder is well documented in the literature. Subjects with AUD have an increased relative risk for bipolar disorder compared to the general population (odds ratio >5)<sup>16</sup>. According to literature data, 40% of cases of maniac episodes seems to be associated with alcohol consumption<sup>49</sup>, and about 50% of hospitalized bipolar patients have a history of hazardous alcohol consumption<sup>50</sup>. In addition, subjects with bipolar disorder have greater chances to develop an alcohol dependence than the general population and for patients with unipolar depression. Table 2 shows studies about the use of anti-epileptic drugs in patients with AUD and psychiatric disorders. Lithium treatment showed no particular efficacy in AUD subjects. A study of 280 patients with AUD, 171 of whom had comorbid depressive or dysthymic disorders, showed no significant differences between the lithium-treated group and the placebo-treated group related to dependence severity and depressive symp-

Table 2. Data for the use of anti-epileptics in patients with psychiatric disorders comorbid with alcohol use disorder.

Drug	Disease	Evidence
Lamotrigine	Bipolar disorder	C2
Gabapentin	Insomnia	C2
Pregabalin	Anxiety disorders	B1
Carbamazepine	Bipolar disorder	C2
Lithium	Bipolar disorder	B2
Lithium	Depression	C2
Valproic acid	Bipolar disorder	B2

toms<sup>51</sup>. A 6-month RCT study was conducted on a sample of bipolar patients with alcohol, cannabis or cocaine dependence, treated with lithium or with lithium/sodium valproate. There were no significant differences related to affective symptoms (manic, depressive, or mixed). Responder patients of both groups, who maintained the psychopathological compensation, also showed a significant reduction in alcohol consumption. Although some patients reported adverse side effects (weight gain, gastrointestinal disorders, polyuria/polydipsia, tremors), no patients stopped the maintenance therapy due to such symptoms<sup>52</sup>. Finally, in a study of 46 adolescents with bipolar I or II disorder and alcohol or cannabis dependence, the weekly urine values of substance abuse were lower in the lithium-treated group compared with placebo<sup>53</sup>. Maremmani et al.<sup>54</sup> hypothesize that anti-euphoric lithium property may have a protective effect over the expansive phase after alcohol detoxification, preventing relapses in patients already in abstinence status, while in active stage it would not emerge a real effectiveness compared to the placebo. Regarding sodium valproate, a Brady pilot study reported a significant improvement in depressive and manic symptoms in AUD bipolar subjects pharmacologically treated, as well as a dependence severity reduction in terms of fewer alcohol intake days<sup>55</sup>. In a recent RCT, 59 patients with bipolar I disorder treated with lithium/valproate or lithium/placebo for 24 weeks were evaluated<sup>56</sup>. The valproate group reported a reduction in heavy drinking days, and lower amounts of daily alcohol drinks compared to the placebo group, as well as significantly lower G-glutamyl transferase blood levels. There were no differences between the two groups compared to the affective symptoms. Several studies and individual case reviews suggest the usefulness of valproate in maintaining alcohol abstinence and craving in patients with psychiatric comorbidity<sup>49</sup>, and in particular in preventing alcohol relapses in patients with bipolar disorder<sup>57,58</sup>. The effectiveness of lamotrigine was evaluated in an open-label study on 28 patients with bipolar disorder and AUD. Psychopathological symptoms, as well as craving indices and daily alcohol consumption, have significantly decreased. There was also a reduction in carbohydrate-deficient transferrin, an indirect index of alcohol intake in the last 2-4 weeks<sup>59</sup>. Compared to topiramate, a drug that in recent years has shown good efficacy in alcohol dependence and craving treatment in AUD patients with no psychiatric comorbidity, there are few evidences of its use in dual diagnosed subjects. Some clinical cases suggest its administration in patients with alco-

hol dependence comorbidity with bipolar disorder<sup>60</sup>. Two separate RCTs by Batki et al.<sup>61,62</sup> investigated the topiramate effectiveness in war veterans patients with PTSD and AUD: they showed an important effect of topiramate in improvement of severity of addiction and PTSD symptoms, in reducing traumatic experiences and in attenuating the post-traumatic hyperarousal. In a 6-week double-blind pilot study, gabapentin showed an improvement in sleep disorders and simultaneously better alcoholic outcome<sup>63</sup>. An open study showed greater effectiveness for gabapentin than trazodone in AUD patients with sleep disorders<sup>64</sup>. In a 71 AUD patients performed RCT, the effectiveness of pregabalin was compared with naltrexone (anti-craving drug), examining craving indices, alcohol withdrawal symptoms, and psychiatric symptoms (measured through the Symptom Check List-90-R<sup>65</sup>). Pregabalin was shown to be more effective than naltrexone in reducing psychopathological symptoms in anxiety, hostility and psychotism areas, and in maintaining abstinence. In particular, pregabalin had better response rates in patients with psychiatric comorbidity, allowing authors to hypothesize that its effectiveness is mediated by the improvement of psychopathological suffering rather than a specific anti-craving action<sup>66</sup>.

### Antipsychotics

In addition to depressive, anxiety and bipolar spectrum disorders, AUD is frequently associated with the presence of a psychotic disorder. According to the epidemiological data provided by the ECA study<sup>16</sup>, AUD comorbidity rates in schizophrenic patients range from 20% to 50%. Table 3 shows the identified papers where an antipsychotic drug was used in AUD patients with comorbid psychotic or bipolar disorders. There are no large-scale RCTs on antipsychotic drug administration in schizophrenic AUD patients. Studies in the literature are mostly based on retrospective data from non-randomized naturalistic researches. Data obtained from the Clinical Antipsychotic Effectiveness Intervention (CATIE) study on schizophrenia make possible to compare olanzapine, quetiapine, risperidone and ziprasidone according to their effectiveness on alcohol dependence. Despite a nonspecific daily intake reduction, no drug

Table 3. Data for the use of antipsychotics in patients with alcohol use disorder comorbid with psychotic or bipolar disorders.

Drug	Disease	Evidence
Clozapine	Schizophrenia	B2
Quetiapine	Bipolar disorder	B1
Olanzapine	Bipolar disorder	B2
Olanzapine	Schizophrenia	C2
Risperidone	Schizophrenia	C2
Aripipazole	Schizophrenia	C2

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was superior to the others in the 18-month follow-up<sup>67</sup>. Clozapine has been investigated as a possible alternative therapy for alcohol-related psychiatric comorbidity. A retrospective study was conducted on 151 patients with schizophrenia or schizoaffective disorder comorbid with substance consumption. Patients with AUD in clozapine therapy showed a significant reduction in the number of alcohol intake days and a significantly higher remission rate of patients in therapy with other drugs<sup>68</sup>. Another retrospective study was performed to compare the effectiveness of clozapine and risperidone in schizophrenic or schizoaffective patients with alcohol and/or cannabis addiction. Remission rates were significantly higher in subjects treated with clozapine<sup>69</sup>. Also the naturalistic study conducted by Kim and co-workers<sup>70</sup> aimed to compare clozapine and risperidone in schizophrenia and AUD treatment. The clozapine group showed a lower hospitalization rate and better remission rates after 2 years. A systematic review of the literature, moreover, suggest clozapine as an atypical antipsychotic specific for alcohol intake reduction in patients with DD. Regarding treatments, AUD patients showed a reduced response to drugs compared to non-dependent patients<sup>71</sup>. Data are available in the literature regarding antipsychotic drug administration in bipolar comorbid disorder with alcohol dependence<sup>72</sup>. Quetiapine is the drug with more evidence in the AUD population, from case reports to controlled trials. A case report describes a bipolar patient who had previously taken lithium-based and sodium-free valproate without treatment, responding to 600 mg quetiapine, with mood stabilization and a significant reduction in daily alcohol intake (from 20 to 5 UA/die)<sup>73</sup>. In a double blind study, 47 patients were treated with quetiapine or placebo for 12 weeks, immediately after a period of alcohol detoxification: 31% of treated group patients maintained the full abstinence from alcohol, compared to 6% in the control group, with a significant reduction in craving measures. Consistent improvements were in patients with type B alcohol addiction (with high familiarity, high dependence severity, frequent psychiatric comorbidity, antisocial behavior) compared to the A-type response<sup>74</sup>. Martinotti et al.<sup>75</sup> gave quetiapine to 28 patients for 16 weeks in an open study on AUD patients with behavioral instability. Compared with the baseline, there have been reported reductions in craving measures, dependence severity, daily alcohol consumption, and psychopathological symptoms. Two RCTs conducted by Brown et al.<sup>76,77</sup> disagreed with these observations. In fact, in these studies the patients already treated for bipolar disorder have not shown significant improvements following add-on quetiapine compared to placebo, either in terms of craving or daily alcohol consumption. Even a double-blind study of Litten et al.<sup>78</sup> on subjects with severe AUD did not show significant differences between quetiapine and placebo, but in this case it should be noted that pharmacological treatment was administered to subjects without psychiatric comorbidity. In a pilot study conducted in 10 patients of alcohol rehabilitation programs, quetiapine was used to treat sleep disorders, with a significant reduction in night awakening<sup>79</sup>. Olanzapine add-on in a sample of 40 patients with bipolar I disorders, hospitalized for mania or mixed status, was effective to reduce alcohol consumption and craving measures<sup>80</sup>. Aripiprazole, in combination with citalopram, was found to

be more effective in reducing craving compared to citalopram monotherapy in two groups of patients with major depressive disorder and AUD. In both groups there was an improvement also in depressive symptoms. In addition, in subjects treated with citalopram/aripiprazole, there was an increase in the anterior cingulate cortex activity, associated with a greater craving control<sup>32</sup>. Despite the frequent evidence for a low adherence to drug therapy in subjects with DD, a common problem in patients with psychotic comorbid disorders, to date, there are few studies in which a long-acting formulation drug was administered. One exception is a recent study by Green and colleagues<sup>81</sup>, where 95 patients with AUD and schizophrenia, recruited into 3 year trials, were treated with risperidone orally or in long-acting injectable formulation. In both groups, pharmacological treatment was relatively ineffective on alcohol dependence symptoms, despite the significant differences noted: the oral therapy group reported alcohol consumption worsening, with greater heavy drinking days, and a greater number of alcohol intake days per week compared to the long-acting drug treated group. There were no significant differences between the two groups compared to the effectiveness of psychotic symptoms. The authors suggest that the only risperidone therapy is not effective on alcohol consumption in schizophrenic patients, and should be associated with a specific addiction management therapy. However, the usefulness and superiority of long-acting administration compared to the oral form, both for addiction severity and for a better therapy adherence, is reported. The work has been resumed and discussed by several authors. Batki<sup>82</sup>, who defines "heroic" the work both for its long duration and the sample size, extends the results to other antipsychotic drugs, arguing that while they may be effective on psychotic symptoms, they do not affect alcohol consumption. Optimal medical therapy should therefore use specific drugs to reduce alcohol consumption and craving. Petrakis, commenting the usefulness of long-acting administration in subjects with poor compliance, suggests to experience similar formulations for anti-craving drugs, particularly for naltrexone<sup>83</sup>.

## DISCUSSION

DD in alcoholology, as well as in other addictions, is a kaleidoscopic and complex clinical entity with a multifactorial origin that cannot be reduced to a unique etiopathogenesis but rather to a pathogenic cascade where family, genetic, epigenetic, developmental, social-environmental, neurobiological and temperamental components, play a role in a synergistic way.

In nosographic terms there is a great debate and a multiplicity of definitions. In our opinion, it seems useful and interesting the recently proposed definition by DSM-5 that overcomes the rigid categorical framework for the benefit of a dimensional enrichment that leaves the primary-secondary dichotomy to the advantage of an induced-independent framework. Precisely, because of the semeiological and therefore the nosographic complexity of this reality, there are gaps and difficulties for an operating and effective framing even in terms of treatment<sup>84</sup>. Daily

clinical practice often does not seem to be equipped to adapt itself to the multiform specificities and patients' needs during their illness history. Although at least 30% of patients with a severe mental disorder show substance dependence (and vice versa), there is an important gap in pharmacological, psychological, social treatments<sup>85-92</sup>. While there are many therapeutic proposals, there is no shared and evidence-based therapeutic strategy that can guide the clinician in his/her work and that can be verified by evidence. Our work is to make a contribution in this regard: in Tables 1-3, we propose the drugs presented in the clinical trials previously described according to different degrees of recommendation using the ranking offered by the European Association for the Study of the Liver (EASL) for the study of the Liver (Table 4)<sup>93</sup>.

The proposal has several limitations:

- diagnoses in the different trials are not homogeneous in terms of the diagnostic criteria applied;
- there are insufficient data to assess the tolerability of psychoactive drugs in AUD patients;
- there are insufficient data on psychopathological crisis management in AUD context;
- endpoints and measurement methods are not homogeneous in the different trials;
- there are very few RCTs.

The proposed contribution, in essence, wants to be a stimulus and an open invitation to implement RCTs to develop evidence-based and shared treatments and to build standardized intervention algorithms suited to individual patient needs during every specific phase of their illness.

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Table 4. Treatments' efficacy grading of both evidence and recommendations (adapted from EASL<sup>93</sup>).

Grading of evidence	Notes	Symbol
High quality	Further research is very unlikely to change our confidence in the estimate of effect and clinical practice	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate and clinical practice	B
Low or very low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate and clinical practice. Any estimate of effect is uncertain	C
Grading of recommendation	Notes	Symbol
Strong recommendation warranted	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weaker recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted. Recommendation is made with less certainty; higher cost or resource consumption	2

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