The Efficacy of Tiapride and Carbamazepine Combination Therapy in Reducing Alcohol Withdrawal Symptoms: A Systematic Review and Meta-Analysis

Authors
Sahar Latifi[1], Thomas Messer[2]

Affiliations
1 Resident of Psychiatry and Psychotherapy, Danuvius Klinik GmbH, Pfaffenhofen an der Ilm, Technischen Universität München, Bavaria, Germany
2 Head of Department, Professor of Psychiatry and Psychotherapy, Danuvius Klinik GmbH, Pfaffenhofen an der Ilm, Technischen Universität München, Bavaria, Germany

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Correspondence
Sahar Latifi, MD
Danuvius Klinik GmbH
Technischen Universität München
Krankenhausstraße 68
85276 Pfaffenhofen an der Ilm, Bavaria
Germany
sahar.latifi@danuviusklinik.de

ABSTRACT

The combination of tiapride (TIA) and carbamazepine (CBZ) as an alternative treatment option to benzodiazepines and clomethiazole has been investigated by several investigations. We performed a systematic review and meta-analysis to further explore the efficacy of this combination in order to render more definite answers whether this combination can be recommendable in the clinical practice. We systematically searched electronic databases including PubMed (MEDLINE), EMBASE, OVID, Cochrane, Google Scholar, and Scopus for human studies. Statistical homogeneity was checked by χ^2 test and I^2 using Cochran heterogeneity statistic. Our analysis showed a significant efficacy of the combination of TIA and CBZ in reducing alcohol withdrawal syndrome (AWS) ($p < 0.0001$, z-value: 4.07). The cumulative analysis illustrated that the favorable efficacy of this combination therapy has been consistent over time. Our study shows that the combination of TIA/CBZ is an effective treatment in management of AWS in patients with alcohol abstinence. However, the safety of this combination could not be proven, so we recommend its prescription after an informed consent.

Introduction

Alcohol withdrawal syndrome (AWS) can cause a life-threatening condition that increases the concerns for the necessity of suitable and rapid treatments. It has been shown that chronic alcohol consumption induces neuroadaptive changes that involve mainly the gamma-aminobutyric acid (GABA) receptors central noradrenaline, dopamine, and glutamate receptors [1, 2]. Studies have shown that a reduced neurotransmission in $GABA_A$ and an enhanced neurotransmission in glutamatergic pathways results in an imbalance between inhibitory and excitatory neurotransmitters [3], which leads to the nervous system hyperactivity [4]. In fact, GABA has an inhibitory effect that suppresses neural activity and thereby it plays an important role in developing the tolerance and inducing the withdrawal syndrome in patients with long-term exposure to alcohol [5]. Recent studies have also shown that a genetic variation in $GABA_A$ receptor subunits affects the risk for developing alcoholism [6]. Furthermore, an increased level of dopamine has been reported in patients with AWS [7]. The involvement of other neuromodulators, such as serotonin and corticotropin-releasing factor, has also been described, which presents the AWS as a complex phe-

nomenon affecting multiple nerve systems [8]. Triggering this complex matrix of receptors and neurotransmitters to reduce the withdrawal symptoms has been a challenging theme in the recent researches. In this field, many combinations of medications have been studied. The most common treatment options are clomethiazole and benzodiazepines. Bonnet et al. [9] compared the efficacy of clomethiazole and clonazepam in a prospective observational study that revealed no significant difference between these 2 medications. A new study by Sychla et al. [10] showed that both diazepam and clomethiazole were equally effective and safe; however, clomethiazole showed a faster effect, so patients treated with clomethiazole were treated significantly shorter. Furthermore, benzodiazepines have become worldwide the first choice of treatment of AWS because clomethiazole-induced respiratory insufficiency has limited its use in clinical practice [11]. A new study in Germany by Verthein et al. [12] showed that oxazepam is as effective as clomethiazole in treatment of AWS. Although benzodiazepines are prescribed vastly in management of AWS [13], many side effects such as memory deficits and interactions with other drugs have been reported frequently [14, 15]. The benzodiazepine-induced additive sedation in combination with alcohol can cause respiratory suppression [16]. Furthermore, benzodiazepines can cause additional addiction problems that also should be taken into consideration [17]. Although some beneficial effects of long-term prescription of benzodiazepines in patients with alcohol dependence have been reported [18], they must be prescribed cautiously in clinical practice. Leggio et al. [19] reported that the addictive properties of benzodiazepines increase the focus on non-benzodiazepine GABAergic medications such as carbamazepine (CBZ), which shows promising effects in clinical studies.

CBZ is an anticonvulsive that is typically used for the treatment of seizure disorders and neuropathic pain. However, it has been shown to be effective, safe, and well-tolerable in treatment of AWS [20–22]. Prince and Turpin [23] reported the beneficial effect of CBZ in patients with alcohol dependence, but adverse effects (for example, dizziness, drowsiness, nausea, and vomiting as the most frequent side effects) and drug interactions may limit its usefulness. CBZ is a potent inducer of hepatic cytochrome CYP3A4 and is also known to be an inducer of CYP1A2, 2B6, and 2C9/19, so it may reduce plasma concentrations of medications mainly metabolized by these cytochromes (for example aripiprazole and tacrolimus) through accelerating their metabolism.

Tiapride (TIA) is a dopamine D2 and D3 receptor antagonist. It is used to treat a variety of disorders including dyskinesia, negative symptoms of psychosis, and agitation and aggression in the elderly [24]. A combination of CBZ and TIA has been shown to effectively reduce the withdrawal symptoms without inducing an additive sedation [25]. Since dopamine hyperactivity has been linked with AWS, TIA's antidopaminergic effects can influence withdrawal symptoms favorably. In this combination therapy, TIA works as an anxiolytic whereas the hallucinations, delirium tremens and epileptic attacks by alcohol withdrawal will be targeted by CBZ. In fact, the therapeutic rational is the combined effect on both seizure risk and psychovegetative symptoms without a significant risk for an abuse. This combination has also been shown to be safe even in outpatient settings [26, 27]. However, lack of definite proofs and meta-analysis above all leads to uncertainties in clinical practices. The aim of this study was to review the literature addressing the efficacy and safety of the combination therapy with CBZ and TIA in treatment of AWS. We also performed a meta-analysis to examine the results of the relevant studies in order to render more definite answers if this combination in the clinical practice is recommendable. To our knowledge, this is the first meta-analysis addressing the efficacy of this combination therapy in patients with alcohol dependence.

Methods

Study design and data collection

This study is a systematic review that summarizes the findings of previous researches addressing the efficacy and safety of CBZ and TIA in treatment of alcohol withdrawal symptoms. We also performed a meta-analysis to compare the outcomes of relevant literature. We systematically searched electronic databases including PubMed (MEDLINE), EMBASE, OVID, Cochrane, Google Scholar, and Scopus for human studies with the following keywords: "triapride" AND/OR "carbamazepin" AND "alcohol withdrawal" OR "alcohol dependence" OR "alcohol abuse." The references of the retrieved articles were also scanned to detect the relevant literature. All potential published studies up to May 2018 have been reviewed.

Study eligibility criteria

The relevant studies evaluating the effect of the combination therapy with TIA and CBZ have been considered as eligible. The inclusion criteria were studies on human subjects, existence of adequate comparative data, and application of standard instruments for assessment of withdrawal symptoms for proper comparison. Primary search of databases with mentioned keywords revealed 290 articles, whereby after exclusion the irrelevant article after initial screening, 7 studies could be selected. The main reasons for exclusion were irrelevance of basic theme, lack of adequate comparative data, lack of application a standard method for assessment the AWS, lack of use of a combination therapy of TIA and CBZ (application of monotherapy), and use of other anticonvulsants in combination with TIA. Among the selected articles, 2 studies were case reports (on only 1single case), so these studies have been also excluded because of lack of the comparative data.

Assessment of alcohol withdrawal symptoms

Most of the involved studies have used the Clinical Institute Withdrawal Assessment for Alcohol (CIWA) for the evaluation of AWS. CIWA or CIWA-Ar (revised version), is a 10-item scale that is used to assess the severity of alcohol withdrawal symptoms. This instrument assesses the 10 common symptoms of alcohol withdrawal (nausea and vomiting, tremor, paroxysmal sweats, anxiety, agitation, tactile disturbances, auditory disturbances, visual disturbances, headache and orientation) [28, 29]. Each item on the scale is scored independently, and the summation of the scores correlates to the severity of alcohol withdrawal symptoms. A mild alcohol withdrawal is defined with a score of ≤ 15, moderate with scores of 16–20, and severe with any score > 20. All items are scored from 0–7, except for the orientation category, which is scored from 0–4. The maximum score is 67.

Statistical analysis

All the statistical analysis was performed using Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ, USA). Statistical homogeneity was checked by χ^2 test and I^2 using Cochran heterogeneity statistic, in which I^2 higher than 75 % represents a heterogenic data. By heterogeneity the random effect model has been used to calculate the weighted mean difference and 95 % confidence interval (CI) [30, 31]. Random effects model enables a proper comparison of data between different studies with little homogeneity with the assumption that the effects being estimated in the different studies are not identical but follow some similar distributions, which makes the synthesis of the information possible. Simulations have shown that this model can provide valid results even under extreme distributional assumptions [32]. This model can also be used in assessment of risk factors in meta-analysis setting [33]. By studies in which no control or comparison groups have been assigned, we used the pre-post model with entering the data of means and standard deviations at the beginning and end of the study. The Rosenthal conservative estimate of 0.7 was used as the pre-post correlation [34]. We have also performed a sensitivity analysis (leave-one-out analysis) to make sure that the results were not influenced by a single study. Leave-one-out meta-analysis involves performing a meta-analysis on each subset of the studies obtained by removing 1 study at a time.

Results

We summarized the major findings of relevant studies assessing the effect or safety of the treatment with TIA and CBZ in patients going through an alcohol detoxification program in ▶ **Table 1**. The combination of TIA/CBZ has been administered in seven studies, in which 6 of them have reported this combination as a safe and effective treatment option. One study evaluated the efficacy and safety of the combination of oxcarbazepine (OXC) and TIA in treatment of AWS, which showed a good efficacy and tolerability in comparison with clomethiazole. Three of the seven studies that tested the combination treatment of TIA/CBZ were open clinical studies without assignment of a control group, so we used the pre-post model in a single group for a proper comparison with other studies. Two studies were case reports that reported a single case, so they could not be entered into the meta-analysis because of different study settings. In 4 studies the severity of the withdrawal symptoms was assessed using the CIWA-Ar scale. This instrument has been widely used for assessment of AWS [44–46]. In only one study the visual analog scale and the Symptom Checklist-90-Revised have been used to assess AWS. However, the assignment of a control group (comparison with clomethiazole and diazepam groups) led to proper assessment of difference between groups, so the evaluation of mean difference and F change enabled us to enter this study in our meta-analysis, too. At the end, 5 studies were included in our analysis. ▶ **Table 2** shows the design and the major outcomes of the included literature.

▶ **Table 3** shows the analysis of heterogeneity with assessment of I^2 along with measurement of tau-squared. Since I^2 was more than 75 % (91.7 %), we used the random effect model to enable a proper integration of study results.

Our meta-analysis, which is shown in ▶ **Fig. 1**, illustrates that the combination of TIA and CBZ could effectively reduce the AWS assessed by CIWA-A. The efficacy of this combination in treatment of withdrawal symptoms was significant ($p < 0.0001$, z-value: 4.07). The cumulative analysis shown in ▶ **Fig. 2** illustrate that the favorable efficacy of this combination therapy has been consistent over time. Moreover, as a part of sensitivity analysis, we performed a leave-one-out sensitivity analysis by removing 1 study at a time to confirm that our findings were not driven by any single study (▶ **Fig. 3**).

Discussion

TIA and alcohol dependence

The favorable effect of TIA in promoting abstinence in patients with alcohol dependency has been reported previously [47]. However, further studies in this field reported contradictory results about the effectiveness of TIA in maintaining alcohol abstinence [48]. Since the dopaminergic hyperactivity has been shown to be related to withdrawal symptoms, the antidopaminergic effect of TIA has been a theme for further investigations assessing the role of this medication in reducing the severity of withdrawal symptoms. TIA demonstrates antidyskinetic and anxiolytic activities [49]. It has also a low potential for interaction with ethanol and low risk of abuse [49]. In this field, Murphy et al. compared the efficacy of a monotherapy with TIA with clomethiazole in patients with alcohol dependence and reported that TIA was more successful in alleviating gastrointestinal and psychological distress but was less effective in preventing hallucinosis [50]. Moreover, studies have shown unsatisfactory results in treating delirium tremens with a monotherapy with TIA [51]. Therefore, its administration in acute alcohol withdrawal should be accompanied by adjunct therapy for hallucinosis and seizures [49]. Not only TIA does not induce the over sedation, but it also does not reduce the memory function, which has been frequently reported by benzodiazepines [52]. TIA selective D2 and D3 dopamine receptor antagonist, whereby its receptor occupancy does not exceed 80 % even at high doses [53]. This explains the reasons why TIA causes rarely side effects such as extrapyramidal symptoms or tardive dyskinesia. This advantage of TIA has been discussed in elderly patients by whom TIA can be used to treat agitation [54] and can improve the clinical symptoms in senile dementia more effectively than risperidone and with fewer adverse effects [55]. The safety of TIA administration is advantageous especially in outpatient setting [26, 27]. Since TIA provides a safe and efficient treatment option, with a good patient compliance and the little risks for abuse, it can be considered to be administered especially in outpatient setting by mild to moderate AWS. Furthermore, it is to mention, that the required dosage in outpatient setting may be lower compared to the dosage given to inpatient withdrawal. In this regard, Franz et al. [35] treated the admitted patients with 300 mg TIA every 4 h up to the maximum daily dosage of 1200 mg. Soyka et al. [26, 27] performed 2 studies in outpatient setting and administered a daily dosage of 300 mg TIA, which shows a lower required dosage in patients with mild to moderate AWS. Lucht et al. [36] treated the admitted patients with a minimum daily TIA dosage of 600 mg and a maximum of 1500 mg, which has been

▶ **Table 1** The major findings of relevant studies assessing the effect or safety of the treatment with TIA, CBZ, or OXC in patients with alcohol dependency.

Study	Year of publication	Setting/design	Methodology	Major findings
Franz et al. [35]	2001	Pilot study	Comparison of combination of TIA and CBZ vs. CLO	The combination of TIA/CBZ was a safe alternative in alcohol detoxification. Vegetative recovery seemed to be faster with TIA + CBZ.
Lucht et al. [36]	2003	Controlled open-label study	Treatment with TIA/CBZ, CLO and DZP in intoxicated vs. non-intoxicated patients	In non-intoxicated patients, the combination of TIA/CBZ was as effective and safe as the other groups. In intoxicated patients, TIA/CBZ was safe but a lack of efficacy has been detected in 18 % of participants.
Martinotti et al. [37]	2010	Randomized, single-blind clinical trial	Comparison of LZP with pregabalin and TIA	All used medications were safe. The efficacy of pregabalin was superior to that of TIA and LZP.
Soyka et al. [26]	2002	Open clinical study	Combination of CBZ/TIA in outpatient alcohol detoxification	CBZ/TIA combination is an effective and safe treatment for outpatient alcohol detoxification
Soyka et al. [27]	2006	Open prospective study	Combination of CBZ/TIA in outpatient alcohol detoxification	Additional evidence that a combination of CBZ/TIA is safe and effective by moderate severity of withdrawal symptoms in an outpatient setting.
Soyka et al. [24]	2006	Pooled analysis (retrospective study)	Pooled analysis in 540 patients treated with the combination of CBZ/TIA	Further evidence that a combination of CBZ/TIA is an effective and safe treatment for alcohol withdrawal treatment.
Croissant et al. [38]	2009	Randomized clinical trial	Comparison of the efficacy of the combination of OXC/TIA and CLO	There was no significant difference in safety, efficacy, and tolerability between the combined treatment of OXC/TIA and CLO. The combination of OXC/TIA is as safe as CLO in an inpatient setting.
Müller et al. [39]	2011	Case series	Combination treatment of Levetiracetam and TIA in 9 alcohol-dependent patients in an outpatient setting	Combination of levetiracetam and TIA was a safe and effective treatment option for mild to moderate withdrawal symptoms in outpatient settings.
Gartenmaier et al. [40]	2005	Case report	Combination of CBZ/TIA in treatment of alcohol withdrawal symptoms in a patient with sleep apnea syndrome	This combination treatment was an effective alternative in alcohol withdrawal without the risk of respiratory depression.
Lepola et al. [41]	1984	Controlled clinical trial	Comparison of TIA vs. chlordiazepoxide in acute alcohol withdrawal	Chlordiazepoxide was significantly more effective in reducing the alcohol withdrawal symptoms in comparison with TIA.
Agricola et al. [42]	1982	A double-blind comparison study	The effect of CBZ vs. TIA in treatment of acute alcohol withdrawal syndrome	Both drugs were equally effective in the treatment of alcohol withdrawal symptoms. CBZ provided faster relief of symptoms
Dieh et al. [43]	2007	Case report	Administration of a combined CBZ and TIA in a 45-year-old alcohol-dependent patient	The interaction between CBZ and TIA caused CBZ intoxication with serum levels up to 19 mg/L. This combination seem not to be safe and should be used with cautious.

CBZ: carbamazepine; CLO: clomethiazole; LZP: lorazepam; OXC: oxcarbazepine; TIA: tiapride.

gradually reduced to a dosage between 100–300 mg after 10 days. Both Franz et al. [35] and Lucht et al. [36] described a TIA/CBZ ratio of 1.5 as the optimal efficient dosage for this combination in inpatient setting. However, the dosage of CBZ used by Soyka et al. was 600 mg in combination with 300 mg TIA in outpatient individuals (TIA/CBZ ration of 0.5).

CBZ in treatment of addiction to alcohol

CBZ has been the most used medication administered as an adjunct therapy in combination with TIA. Not only can CBZ be used as prophylaxis for epileptic seizures, but it also can reinforce the alleviation of psychotic and vegetative symptoms of alcohol withdrawal when combined with TIA [35]. Various mechanisms of CBZ including inhibition of dopamine synthesis and modulation of glutaminergic, GABAergic, adrenergic, and cholinergic systems have been described so far [56, 57]. Mariani and Levin [58] mentioned in their study the necessity of alternatives to benzodiazepines for the pharmacological treatment of alcohol-related disorders particularly in outpatient setting. The favorable effect of CBZ in preventing withdrawal seizures and delirium tremens has been shown previously [59]. Seifert et al. [60] compared the efficacy of CBZ with clomethiazole in alcohol withdrawal. In this study CBZ was as effective as clomethiazole in reducing the initial withdrawal symptoms such as tremor, perspiration, and psychomotor agitation. Moreover, patients treated with CBZ showed significantly better verbal memory performance in comparison with clomethiazole [60]. Malcom et al. [61] compared the effect of lorazepam and CBZ in outpatient alcohol withdrawal and showed that both drugs were equally effective. However, CBZ is associated with lots of drug interactions, so other studies have recommended valproate as a better alternative to CBZ regarding tolerability [62]. A

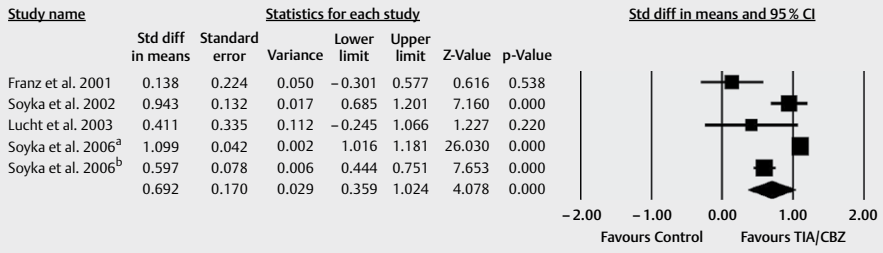
▶ **Table 2** Sample size and outcome measures of the studies included in our meta-analysis.

Study	TIA/CBZ group			Comparison group (CLO or BZD)		
	CIWA-A mean ± SD at the beginning of the study	CIWA-A mean ± SD at the end of the study	Sample size	CIWA-A mean ± SD at the beginning of the study	CIWA-A mean ± SD at the end of the study	Sample size
Soyka et al. [26] 2002	18.29 ± 4.2	14.64 ± 2.93	50	No comparison group		
Soyka et al. [24] 2006	12.3 ± 8.3	2.6 ± 2.4	540	No comparison group		
Soyka et al. [27] 2006	5.0 ± 4.1	2.4 ± 1.2	116	No comparison group		
Franz et al. [35] 2001	21.0 ± 14.0	1.0 ± 3.2	40	20.0 ± 12.0	1.5 ± 4.0	40
Lucht et al. [36] 2003	Mean change: 0.29 F: 1,534		26	Mean change: 0.35 P: 0.224		14

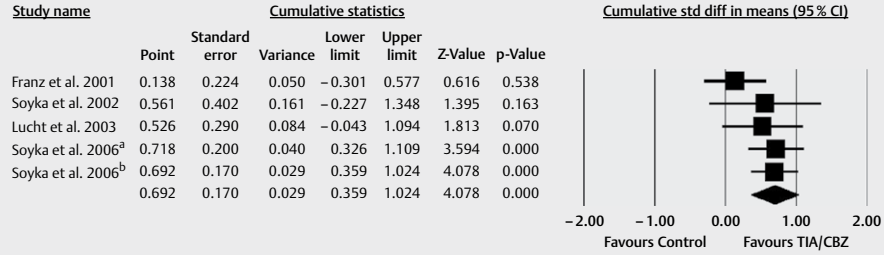
BZD: benzodiazepines; CBZ: carbamazepine; CIWA-A: Clinical Institute Withdrawal Assessment for Alcohol; CLO: clomethiazole; TIA: tiapride.

▶ **Table 3** The test of heterogeneity among the included studies as calculated by χ^2 test and I^2 using Cochran heterogeneity statistic.

Model	Test of null (2-tailed)		Heterogeneity	Tau-squared			
	z-value	p-value	I^2	Tau-squared	Standard error	Variance	Tau
Fixed	27.21	< 0.0001	91.76	0.115	0.125	0.016	0.340
Random	4.07	< 0.0001	-	-	-	-	-

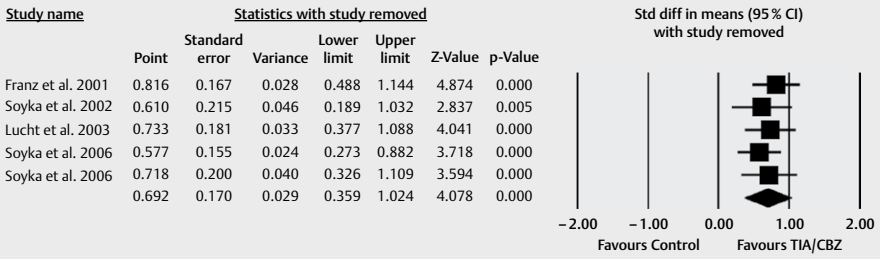


▶ **Fig. 1** Forest plot of the basic analysis using the random effect model. **a** reference number 24, **b** reference number 27.



▶ **Fig. 2** Forest plot of the cumulative analysis using the random effect model to illustrate the stability of outcomes through time. **a** reference number 24, **b** reference number 27.

literature review performed by Prince and Turpin [23] failed to approve the safety of CBZ application in alcohol withdrawal. However, the interaction between CBZ and alcohol remains still unclear. In this regard, Piekoszewski et al. [63] assessed the effect of ethanol on the pharmacokinetic and pharmacodynamic of CBZ in epileptic patients with alcohol dependence. Their study showed that ethanol does not influence the pharmacodynamic of CBZ in acute drug intoxication. Schick et al. [64] reported that both CBZ and OXC were similarly effective in stabilization of vegetative parameters and improvement in the cognitive processing speed. However, this study showed the beneficial effect of OXC in comparison with CBZ because of less drug interactions [64]. Nevertheless, studies have shown contradictory results regarding the usefulness of OXC in alcohol withdrawal. In this regard, Koethe et al. [65] found no significant difference in normalization of vegetative parameters, craving, or improvement of psychopathological parameters between OXC and placebo in treatment of AWS. Since OXC reduces the glutamatergic transmission at corticostriatal synapses, it has been supposed that this medication can have favorable effect in maintaining abstinence in patients with alcohol dependence. Croissant et al. [66] showed that the abstinence



▶ **Fig. 3** Leave-one-out study analysis as a component of sensitivity analysis showing that the findings were not driven by any single study.

duration was similar between patients treated with OXC and those treated with acamprosate. Furthermore, Martinotti et al. [67] demonstrated a favorable significant efficacy of high dosage of OXC (1500–1800 mg/day) in prevention of alcohol-relapse, whereas the lower dosage of OXC showed a weaker effectiveness that was comparable to naltrexone. Since OXC exerts mood stabilization effect, some studies have discussed that the favorable influence of OXC in preventing relapse in alcohol dependence is because of its positive effects on comorbid psychiatric disorders [67]. The mechanism of action of OXC is not yet fully understood. Some studies have also reported a dopaminergic effect if OXC which has caused rarely even psychotic symptoms [68]. However, OXC has been shown to be still a valuable alternative to benzodiazepines because of its better safety profile than classical anticonvulsant drugs and the absence of addictive properties [69, 70].

Safety of the combination of TIA and CBZ in treatment of alcohol withdrawal symptoms

Until now, studies have shown a good tolerability of this combination. However, some case reports have shown unwanted adverse effects of this treatment, so it should still be prescribed with caution. Diehl et al. [43] report a CBZ intoxication in a patient treated with the combination of CBZ and TIA. This result shows that the metabolism of CBZ could have been blocked or decelerated by TIA. There are still limited investigations addressing the interactions between TIA and other drugs. In this regard, Nozaki et al. [71] reported a case of neuroleptic malignant syndrome (NMS) induced by a combination therapy with tetrabenazine and TIA in a patient with Huntington's disease at the terminal stage of recurrent breast cancer. Another case of NMS in an alcoholic patient who received TIA has also been reported, which had led to patient's demise [72]. Furthermore, another study showed an induced Parkinsonism with a combination of TIA and donepezil since the cholinergic effect of donepezil combined with antidopaminergic effect of TIA had caused an acetylcholine/dopamine imbalance [73]. These reports show that the adverse effects of TIA, although rare, can cause life-threatening situations, although there are numerous studies that support the safety and effectiveness of this drug in management of alcohol dependence. In this field, Shaw et al. [74] reported that self-esteem and the subjective satisfaction with life can also be improved by TIA in alcoholic patients. The good tolerability of this medication and low risk of side effect have been reported frequently [74–77]. All these studies, inclusive our meta-analysis, prove that TIA can play an important role management of alcoholism. However, its prescription should be initiated after the patients' informed consent.

This study

In our study, we reviewed the studies that had assessed the combination of TIA and CBZ as a possible alternative for benzodiazepines and clomethiazole. Our meta-analysis shows that this combination can reduce the withdrawal symptoms effectively ($p < 0.0001$). These results show that TIA and CBZ can effectively complete and intensify each other's influence in reducing AWS to treat vegetative symptoms as well as providing a good protection against epileptic attacks by increasing the seizure threshold. According to Franz et al. [35], the combination of TIA/CBZ could reduce the occurrence of seizures more effectively compared to clomethiazole. Moreover, the effect of TIA/CBZ has been reported to be faster than clomethiazole [35].

In our meta-analysis, we could not analyze or compare the dosages used in each study since we have evaluated the efficacy of the general prescribed treatment in comparison with a control group in that single study. Our analysis showed that the applied treatment with the mentioned dosage exerts a significant effect in reducing AWS. However, it seems that the less severe vegetative symptoms in outpatient cases lead to lower required dosage of TIA, whereby the CBZ dosage seems to be similar between inpatient and outpatient settings.

Our meta-analysis was only able to approve the efficacy of combination of TIA/CBZ as an appropriate treatment option, whereas the safety of its administration still has to be proven by further investigation.

Conclusion

Our study shows that the combination of TIA/CBZ is an effective treatment in management of AWS in patients with alcohol abstinence. However, the safety of this combination could not be proved, so we recommend its prescription after an informed consent. In cases of intolerance, OXC is a valuable alternative to CBZ, which can be taken into consideration.

Conflicts of Interest

Prof. Dr. Thomas Messer received honoraria from Janssen-Cilag, Ferrer, Otsuka/Lundbeck and Bayer Vital. Dr. Sahar Latifi declares no conflicts of interest.

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