



# Anticraving therapy for alcohol use disorder: A clinical review

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## Abstract

**Aim:** In this review, the author focused on anticraving therapy for alcohol use disorder (AUD) defined by DMS-5. A comprehensive review was carried out on the available published papers on anticraving drugs for treating AUD patients.

**Methods:** The author described all drugs with anticraving benefits for treating AUD patients approved by the Food and Drug Administration of the United States (US FDA) and European Medicines Agency of the European Union. Then, the commonly prescribed anticraving drugs and those under development were also described.

**Results:** The US FDA-approved anticraving drugs included acamprosate and naltrexone, and those approved by European Medicines Agency were gamma-hydroxybutyrate and nalmefene. The author also highlighted topiramate, gabapentin, ondansetron, LY196044, ifenprodil, varenicline, ABT-436, mifepristone, citicoline, and baclofen. The putative mechanisms of action of and the use in clinical practice of those anticraving drugs were also described.

**Conclusion:** Although slowly developing, the field of anticraving drugs is getting into shape as a promising entity of a pharmaceutical class of drugs. Then, the author addressed on the underused issues of those recommended, and suggested anticraving drugs by the practice guideline of the American Psychiatric Association. The author urges that clinicians should be more “adventurous” in prescribing those promising drugs because benefits of those anticraving drugs are far-outweighing the possible side effects of anticraving drugs, or the harms of untreated AUD itself.

## KEYWORDS

acamprosate, gabapentin, gamma-hydroxybutyrate, ifenprodil, nalmefene, naltrexone, topiramate

## 1 | INTRODUCTION

“No, No! The adventures first,” said the Gryphon in an important tone: “Explanations take such a dreadful time”

Lewis Carroll, *Alice in Wonderland*

The review on the topic “pharmacotherapy of alcoholism” for my first time was in 1991.<sup>1</sup> Upon the invitation of H. Hosaki *sensei*, then chair professor of Department of Neuropsychiatry at Keio

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University, the author presented in 1990 a lecture organized by Keio Psychiatrists' Alumni Organization on this topic. The host's intention was for me to share the state of the arts knowledge of drug treatments for alcoholism of the United States of America to Japanese psychiatric colleagues.

At the 2017 annual meeting of the American College of Neuropsychopharmacology in Palm Springs, California, USA, the author was invited from K. Ikeda *sensei*, the President of Japanese Society of Neuropsychopharmacology, to write an article for Neuropsychopharmacology Reports. I accepted then the invitation right away. After a 4-month consideration, I finally decided to choose the topic of anticraving therapy for alcoholism, to give myself a chance to revisit the topic that I have been involved at since late 1970s.

Compared to those 27 years ago, all drugs except disulfiram for treating alcohol use disorder (AUD) patients' "intense drug craving" are new to the author.<sup>1,2</sup> In 1991, disulfiram was the only drug approved by the Food and Drug Administration of the United State of America (US FDA, [www.fda.org](http://www.fda.org)) specifically for AUD patients.<sup>1</sup> But disulfiram is not a drug to give anticraving benefits for AUD patients.

In this review, the author started to describe the diagnosis "AUD" in the 2013 framework of American Psychiatric Association's Diagnostic and Statistical Manual for Mental Disorders, the Fifth Edition (DSM-5).<sup>2</sup> Anticraving drugs include those approved by the US FDA and European Medicines Agency, as well as those commonly prescribed or those in pharmaceutical pipeline for drug development. Finally, the author covered putative mechanism of actions of those drugs, described their prescriptions in clinical practice, and addressed the issue of underuse in prescribing this class of anticraving drugs. This review was intended to promote the awareness of AUD patients, and to urge clinicians to prescribe those underused but readily available anticraving drugs for treating AUD patients.

## 2 | THE DIAGNOSIS OF ALCOHOL USE DISORDER IN DSM-5

The chapter "substance-related (and additive) disorders" (pages 481-589) of APA's DSM-5,<sup>2</sup> describes 11 substance-related disorders and one nonsubstance related disorder (gambling). On page 482 of DSM-5,<sup>2</sup> a table "diagnoses associated with substance class" lists 12 diagnoses—psychotic, bipolar, depressive, anxiety, obsessive-compulsive and related, sleep, sexual dysfunctions, delirium, neurocognitive, substance use disorders, as well as substance intoxication, and substance withdrawal. Each diagnosis can be applied to all classes of substances included in the chapter "substance-related disorders" except caffeine (page 483 of DSM-5).<sup>2</sup> Tea drinking or coffee drinking in DSM-5,<sup>2</sup> in author's opinion, is recognized as a culturally acceptable human behavior rather than a psychiatric disorder.

Those 12 substance-related disorders are divided into two groups of diagnoses—substance use disorder (one diagnosis totally) and substance-induced disorders (11 diagnoses totally). In further description, substance use disorder has "an underlying change in

brain circuitry that may persist beyond detoxification, particularly in individuals with severe disorders. The behavioral effects of these brain changes may be exhibited in 'repeated relapses and intense drug craving' when the individuals are exposed to drug-related stimuli" (page 483 of DSM-5).<sup>2</sup>

The pharmacologic treatments for substance-related disorder are intended to manage various symptoms and signs of different diagnoses due to effects or complications from the use of substances. The drug treatments for various "substance use disorder" (listed as a diagnosis number 10 of 12 diagnoses for various substances (page 482 of DSM-5).<sup>2</sup> The diagnosis "AUD" in DSM-5 is the focus in this review.

## 3 | TWO ANTICRAVING DRUGS APPROVED BY US FDA FOR TREATING PATIENTS WITH AUD

The US FDA ([www.fda.org](http://www.fda.org)) has so far approved three drugs—disulfiram oral dose in 1951, naltrexone in oral use in 1994 and long-acting injection use in 2006, and acamprosate in oral use in 2004—for patients with AUD after stopping their use of alcohol.

After ingestion, alcohol is metabolized into acetaldehyde through the oxidation process with the enzyme alcohol dehydrogenase in the presence of zinc ions. This is a rate-limiting step. Then, the metabolite acetaldehyde is instantly converted into acetic acid through the enzymatic action of acetaldehyde dehydrogenase. But this step can be inhibited by disulfiram. For the patients who are "pre-medicated" with disulfiram, consumption of alcohol causes rapid accumulation of acetaldehyde in the body, producing disulfiram-ethanol reaction (DER). The patients with DER experience terribly uncomfortable symptoms and signs, such as facial flush, headache, breathing difficulty, nausea, vomiting, sweating, thirsty feeling, chest pain, dizziness, palpitations of the heart, restlessness, exhaustion, photophobia, confusion in consciousness level, ... The severe DER can even cause bradypnea, shock, heart exhaustion, stupor, convulsion, and death.<sup>1,3</sup>

The role of disulfiram is to premedicate this compound to create patients' fear for developing DER to deter them from drinking alcohol. In the sense of behavior science, the treatment mechanism of action is negative reinforcement (i.e., punishment) if the patients decide to drink. Although disulfiram medicated-patients still have the craving to drink alcohol, they are afraid of drinking due to the threat of developing DER.

The 2018 APA practice guideline suggests (2C) that disulfiram be offered to moderate to severe AUD patients (a) who have a goal of achieving abstinence, (b) who prefer disulfiram or are intolerable to or have not responded to naltrexone and acamprosate, (c) who can understand the risks of alcohol consumption while taking disulfiram, or (d) who have no contraindications to use it.<sup>4</sup> To note, the recent APA guideline<sup>4</sup> uses the word "suggests," which is 2C in suggestion level. In my opinion, the APA guideline suggests 2C in suggestion ranking for disulfiram, recognizing that disulfiram is not to be prescribed as the first line drug for AUD patients.



### 3.1 | Acamprosate is intended to be an anticraving drug to stop alcohol drinking by US FDA

Acamprosate, a glutamate agonist, is derived from amino acid, taurine.<sup>5</sup> In a double-blind, placebo-controlled study in Germany, acamprosate has been found to have anticraving property to prevent recovered alcoholics from drinking alcohol again.<sup>5</sup> Under the pressure of families of alcoholic patients, the US FDA-approved acamprosate for the American market in 2004. At that time of approval, acamprosate had already been on the market of 37 countries in the world.<sup>3</sup>

The anticraving efficacy of acamprosate has been proven not as good as expected in patients' tendency for the time to first drink and the time to relapse.<sup>6</sup> In the double-blind, placebo-controlled comparison study of combining acamprosate and naltrexone for alcoholic patients, the investigators found that anticraving property of acamprosate plus naltrexone is better than acamprosate alone, but not better than naltrexone alone.<sup>6</sup> In prospective, 6-week, randomized double-blind studies in America<sup>7</sup> and in Australia,<sup>8</sup> two groups of investigators independently found that naltrexone but not acamprosate has anticraving property against alcohol drinking.

In a recent randomized, double-blind, placebo-controlled clinical trial of acamprosate in alcohol-dependent individuals with bipolar disorder, the investigators found that acamprosate group has not been detected any better treatment difference in alcohol drinking compared to the placebo group, and that no differences exist in depressive symptoms, manic symptoms, or adverse events between acamprosate and control groups.<sup>9</sup> In another randomized, double-blind, placebo-controlled, parallel group design of acamprosate in two American family medicine settings (North Carolina and Wisconsin), the results of the clinical trial showed that acamprosate has not been found to have anticraving effects in measuring percent days of abstinence and percent heavy drinking days.<sup>10</sup>

The 2018 APA practice guideline recommends (1B) that acamprosate be offered to patients with moderate to severe AUD, (a) who have a goal of reducing alcohol consumption or achieving abstinence, (b) who prefer pharmacotherapy or have not responded to nonpharmacological treatment alone, or (c) who have no contraindications to use it.<sup>4</sup> To note, the use of the word "recommends," which is 1B in recommendation ranking level.

### 3.2 | Naltrexone as an anticraving agent to stop alcohol drinking by US FDA

Naltrexone, an opioid receptor antagonist, is mainly blocking  $\mu$  opioid receptors,<sup>3</sup> although it also blocks on  $\kappa$  opioid receptors to a lesser extent, but on  $\delta$  opioid receptors insignificantly. In a 12-week, randomized, double-blind, placebo-controlled study on 72 alcoholic patients,<sup>11</sup> patients on 50 mg/d of naltrexone have been found to have less craving, decreased frequency of alcohol drinking time, and decreased frequency of patients' abnormal hepatic gamma-glutamyl transpeptidase (gamma GT) enzyme. In another double-blind, placebo-controlled study on 97 alcoholic patients,<sup>12</sup> patients on

50 mg/d of naltrexone have been found to have less patients' alcohol drinking days and less problem resulted from their drinking. As stated previously, Anton et al<sup>7</sup> in America and Morley et al<sup>8</sup> in Australia have independently confirmed the anticraving efficacy of naltrexone against alcohol drinking.

Based on findings of those study results, naltrexone has more reliable anticraving benefit than acamprosate. Similar to acamprosate in recommendation level (1B), naltrexone has also been recommended in the 2018 APA practice guideline for the pharmacological treatment of AUD patients.<sup>4</sup> The recent APA practice guideline recommends that naltrexone be offered to patients with moderate to severe AUD, (a) who have a goal of reducing alcohol consumption or achieving abstinence, (b) who prefer pharmacotherapy or have not responded to nonpharmacological treatment alone, or (c) who have no contraindications to use it.<sup>4</sup>

## 4 | TWO ANTICRAVING DRUGS APPROVED BY EUROPEAN MEDICINES AGENCY FOR TREATING PATIENTS WITH AUD

### 4.1 | Gamma-hydroxybutyrate

$\gamma$ -Hydroxybutyrate (GHB) is thought to be a weak partial agonist at the gamma-aminobutyric acid B (GABA<sub>B</sub>) receptors, and is clinically used for treating narcolepsy.<sup>13</sup> GHB has been found to be effective for treating AUD in a placebo-controlled clinical trial conducted in Europe.<sup>13</sup> Following a daily oral administration of 50 mg/kg for a 6-12 month, multicenter, open-labeled trial, the investigators found that 78% of GHB-medicated patients have complete abstinence during drug administration and reduced in craving for alcohol.<sup>14</sup>

$\gamma$ -Hydroxybutyrate has been approved for AUD treatment in several European countries.<sup>13</sup> Swift and Aston<sup>13</sup> in 2015 suggested that GHB acts as an alcohol substitute, reducing craving for alcohol and preventing alcohol withdrawal. But the abuse potential of GHB has been noted in some European studies, and the medication is frequently abused in the United States.<sup>13</sup> In prescribing GHB, clinicians need to carefully choose patients who are likely to be adherent to dosing recommendations, and to closely monitor the use of GHB.<sup>15,16</sup>

In author's opinion, prescribing GHB for an AUD patient needs to be seen as a kind of replacement therapy, such as methadone for patients with opioid use disorder, or nicotine patch for patients with tobacco use disorder.<sup>4</sup> The readers of this review are cautioned in prescribing GHB as an anticraving drug for AUD patients.

### 4.2 | Nalmefene

Nalmefene is a  $\mu$ -opioid antagonist and partial  $\kappa$  agonist.<sup>17</sup> Nalmefene has been approved by the US FDA only for opioid overdose (www.fda.org). The efficacy of nalmefene for anticraving therapy for AUD patients has not been shown to be any better than placebo in clinical trials in the United States.<sup>18</sup> But it did well in three multi-site



trials in Europe, where nalmefene has been approved for AUD patients by the European Medicines Agency.<sup>17,18</sup>

In a randomized, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in AUD patients, the efficacy analyses showed a superior effect of nalmefene compared to placebo in having less heavy drinking days from baseline to month 6.<sup>19</sup> In a subgroup analysis of patients with high/very high drinking risk levels at screening and at randomization (the target population), nalmefene has been found to have a decreased total alcohol consumption at month 6, and decreased both heavy drinking days and total alcohol consumption at month 13 in nalmefene patients compared to those in placebo group.<sup>20</sup>

## 5 | PROMISING ANTICRAVING DRUGS NOT APPROVED BY US FDA OR EUROPEAN MEDICINES AGENCY FOR TREATING PATIENTS WITH AUD

### 5.1 | Topiramate

Topiramate, a sulfamate in structure and a fructopyranose derivative,<sup>21</sup> was developed serendipitously as an antiepileptic drug ([www.fda.org](http://www.fda.org)) when it was originally being tested whether it has hypoglycemic properties.<sup>3</sup> Besides the antiepileptic property, the US FDA also approved it for the indication of treating migraine headache ([www.fda.org](http://www.fda.org)).<sup>3,21</sup> Its mechanism of actions is relatively unknown, but has been studied to show that it acts with  $\gamma$ -aminobutyric acid (GABA). Topiramate also reduces the action of excitatory neurotransmitters through kainate and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and decreasing the action of carbonic anhydrase.<sup>3</sup>

In a randomized, double-blind, placebo-controlled clinical drug trial, topiramate has been found to have anticraving properties against alcohol drinking.<sup>22</sup> In a double-blind, placebo-controlled drug trial, patients on 300 mg/d of topiramate have been found to have lower drinking quartiles on percentage of heavy drinking days, and improvements in all measures of psychosocial functioning (improved overall well-being and better overall life satisfaction), compared to those on placebo.<sup>23</sup> In another 14-week, randomized, double-blind, placebo-controlled trial, topiramate at the dosage level of 300 mg/d has been found again to have decreased patients' total drinking days compared to those who were on placebo.<sup>24</sup> Furthermore, topiramate in a double-blind drug trial has shown to have its anticraving effect for patients with comorbid dependence on alcohol and cocaine.<sup>25</sup>

The recent APA practice guideline suggests (2C) that topiramate be offered to moderate to severe AUD patients (a) who have a goal of reducing alcohol consumption or achieving abstinence, (b) who prefer topiramate or have not responded to naltrexone and acamprosate, or (c) who have no contraindications to use it.<sup>4</sup> To note, the APA practice guideline uses the word "suggests" instead of "recommend" with 2C level in suggestion level here. This is probably to reflect topiramate's nonapproval status for AUD from US FDA, although it has been found to have anticraving benefit for AUD patients long time ago.<sup>22-25</sup>

### 5.2 | Gabapentin

Gabapentin was originally developed as an analog of GABA, which is the major inhibitory neurotransmitter in the brain.<sup>26</sup> Not acting on GABA precursor, agonist or antagonist, gabapentin increases brain and intracellular GABA by an amino acid active transporter at both the blood-brain barrier and many enzymatic regulation mechanisms. Further glutamate metabolism is also modulated by gabapentin.<sup>26</sup> Gabapentin has been approved by the US FDA for the adjunctive treatment of complex partial epilepsy with and without generalized seizures and for treating neuralgia after infection of herpes zoster, diabetic neuropathy, and restless leg syndrome ([www.fda.org](http://www.fda.org)).

In a 28-day, placebo-controlled, randomized, double-blind clinical trial, investigators found that gabapentin (300 mg, twice daily) can reduce AUD patients' number of drinks per day, the mean percentage of heavy drinking days, craving for alcohol, and increased percentage of days of abstinence in the gabapentin group than those in the placebo group.<sup>27</sup> In a 12-week, randomized, placebo-controlled, a dose-dependent manner of gabapentin (0, 900, 1800 mg/d) and concomitant manual-guided counseling, gabapentin has been found to improve the rates of abstinence and no heavy drinking, particularly in the 1800 mg/d group.<sup>28</sup>

According to a medical news report of JAMA,<sup>18</sup> Lyon reported that a new 6-month "pivotal" randomized, double-blind, placebo-controlled clinical drug trial of 348 patients at 10 US sites on gabapentin's anticraving efficacy was just completed, and that the full study is to be published in a professional journal. In this trial with two studies, 1200 mg of gabapentin enacarbil in a 4-week treatment has been reported to have "favorable" no heavy drinking days compared to placebo. In a smaller, 3-month study of gabapentin was completed with 85 of 150 participants, gabapentin at 1800 mg/d has also been reported to have "favorable" rate of abstinence and no heavy drinking compared to placebo.<sup>18</sup>

Similar to topiramate in suggestion status (2C), gabapentin has also been suggested in the recent APA practice guideline for the pharmacological treatment of AUD patients.<sup>4</sup> The guideline suggests that gabapentin be offered to moderate to severe AUD patients (a) who have a goal of reducing alcohol consumption or achieving abstinence, (b) who prefer gabapentin or have not responded to naltrexone and acamprosate, or (c) who have no contraindications to use it.<sup>4</sup> To note, the APA practice guideline uses the word been "suggested" instead of been "recommended" with 2C level in suggestion level here. This is probably to reflect gabapentin's nonapproval status for AUD from US FDA, although it has been reported to have "favorable" anticraving benefits pending for the consideration for an approval by the US FDA.<sup>18</sup>

### 5.3 | Ondansetron

Ondansetron is a serotonin 5-HT<sub>3</sub> receptor antagonist.<sup>3</sup> In a randomized controlled clinical trial, ondansetron has been found to reduce self-reported drinking.<sup>29</sup> Patients who received ondansetron



at 4  $\mu\text{g}/\text{kg}$  twice per day have been found to have fewer drinks per day, greater percentage of days of abstinence, and total number of days abstinent per study week in AUD patients with early onset of alcohol drinking.<sup>29</sup> A meta-analysis of seven trials showed that selective serotonin reuptake inhibitors do not effectively treat AUD patients who do not have comorbid depression.<sup>30</sup>

The recent APA practice guideline does not mention any endorsement for the use of any 5-HT<sub>3</sub> antagonist for anticraving use against alcohol drinking.<sup>4</sup> At the same time, the guideline also does not recommend for any antidepressant medications for treating AUD patients unless a co-occurring disorder exists for which an antidepressant is an indicated treatment.<sup>4</sup> In the United States, ondansetron is only available in injectable formulation for controlling nausea and vomiting for cancer patients receiving chemotherapy ([www.zofran.org](http://www.zofran.org)).

## 5.4 | LY2196044

LY2196044 is an opioid antagonist.<sup>31</sup> In phase 2, 16-week, multicenter, outpatient, randomized, double-blind, parallel, and placebo-controlled trial for patients (N = 375) with alcohol-dependent, treatment-seeking adults, the investigators found that LY2196044-medicated patients have in both decreased mean number of drinks per day and reduced drinks per day than placebo patients.<sup>31</sup> But to my best knowledge, I have not seen any further trial pursuing its pharmaceutical development, and I have not found any article on LY2196044 after the publication of the above-named trial<sup>31</sup> in a Pubmed search.

## 5.5 | Ifenprodil

Ifenprodil which is an inhibitor of N-methyl-D-aspartate (NMDA) receptor,  $\alpha$ -1 adrenergic receptor, and G protein-activated inwardly rectifying potassium (GIRK) channel,<sup>32,33</sup> is commonly used as a vasodilator to improve patients with peripheral vascular disease symptoms such as dizziness secondary to brain infarction or brain bleeding in Japan. In 1999, Suzuki et al<sup>33</sup> found that pretreatment with ifenprodil (5, 10, 20 mg/kg, intraperitoneally) suppresses the place preference produced by morphine in a dose-dependent manner in laboratory mice. To paraphrase the study finding, mice have stayed in their own chosen places in the cage under morphine medication, but they do not care much where they stay in the cage after their being premedicated with ifenprodil.

In 2011, a preliminary clinical trial reported that AUD patients treated with GIRK channel inhibitor has been found to improve their alcohol abstinence and negative expectancy for alcohol compared to those treated with non-GIRK channel inhibitor.<sup>34</sup> In a recent study, the investigators found that AUD patients treated with ifenprodil (60 mg/d) for 3 months have lower alcohol use score compared to those treated with Cinal (a control study drug).<sup>35</sup> This study was randomized, controlled, rater-blinded clinical trial. The investigators suggested that double-blind trials in collaboration with pharmaceutical companies would be important in the future.<sup>35</sup>

## 5.6 | Additional drugs

The National Institute on Alcohol Abuse and Alcoholism ([www.NIAAA.org](http://www.NIAAA.org)) of the United States is the lead agency for US research on AUD,<sup>18</sup> and other health and developmental effects of alcohol use. The NIAAA also gives grants to support national and international investigators to conduct basic and clinic studies on AUD. In a recent article in the medical news column of JAMA,<sup>18</sup> Lyon has highlighted gabapentin and some going or completing clinical trials on anticraving drugs for AUD patients under the support from NIAAA.

### 5.6.1 | Varenicline

Varenicline, a partial agonist for  $\alpha$ 4 $\beta$ 2 nicotinic acetylcholine receptor subtype (nACh),<sup>3</sup> has been shown to be the most effective pharmacotherapy for smoking cessation. In a randomized, 12-week, control trial, varenicline has been found to higher smoking abstinence rate at weeks 1, 12, and 24 in varenicline group compared to placebo group.<sup>36</sup> Furthermore, in smokers with AUD, varenicline has also been found to lower mean drinks per drinking day at week 12, suggesting that varenicline can decrease alcohol consumption in this population of smokers.<sup>36</sup>

### 5.6.2 | ABT-436

ABT-436 is an orally active, highly selective vasopressin V1B receptor antagonist which was under development by Abbott Laboratories and AbbVie.<sup>37</sup> In phase 2, 4-site, 12-week, double-blind, placebo control clinical trial of ABT-436, AUD participants (N = 150) received ABT-436 or placebo, and a computerized behavioral intervention.<sup>18,37</sup> The ABT-436 (800 mg/d) group has been found to have significantly greater percentage of abstinent days, and to smoke significantly less cigarettes compared to placebo groups.<sup>37</sup> But the between-group differences do not exist in percentage of heavy drinking days, alcohol craving, and alcohol-related consequences, suggesting there may be value in testing medications targeting the vasopressin receptor in alcohol-dependent patients with high stress.<sup>37</sup>

### 5.6.3 | Mifepristone, or RU-486

Glucocorticoid receptor antagonist better known as mifepristone, or RU-486, has also been found to reduce alcohol intake in humans. Like ABT-436, it works on the stress system by regulating the amygdala.<sup>18</sup> A clinical trial assessing the efficacy of mifepristone in treating AUD is currently underway at Brown University.<sup>18</sup>

In a published clinical trial protocol on mifepristone from the United Kingdom,<sup>38</sup> the investigators planned to recruit AUD patients after a recent detoxification from alcohol and randomize them to receive 600 mg a day of mifepristone (200 mg morning, afternoon and evening) for 7 days and 400 mg for the subsequent 7 days (200 mg morning and evening) or the equivalent number of placebo tablets for 14 days. Study participants will remain in the trial for



4 weeks (at least 2 weeks as an inpatient) and will be followed up at 3, 6 and 12 months postrandomization. Their plan to measure study patients' cognitive function at week 3 and 4 after cessation of drinking, symptoms of depression over the 4 weeks after cessation of drinking, the acute phase of alcohol withdrawal, alcohol craving, symptoms of protracted withdrawal, maintenance of abstinence, and levels of relapse drinking at follow-up.<sup>38</sup> We are still looking forward to seeing the role of glucocorticoid Type II receptor activation in outcome measures including the anticraving efficacy from mifepristone.

#### 5.6.4 | Citicoline

A well-tolerated, over-the-counter supplement, to modulate cholinergic systems. In a previous clinical trial, investigators found that citicoline is effectively to reduce cocaine use in cocaine use disorder patients with bipolar I disorder.<sup>39</sup> Results of a 12-week, placebo-controlled trial showed that citicoline reduces heavy drinking, suggesting that it may help not to initiate any substance abuse by enhancing cognitive function and better decision-making through increased acetylcholine signaling.<sup>18</sup>

#### 5.6.5 | Baclofen

An agonist of metabotropic  $\gamma$ -aminobutyric acid B (GABA<sub>B</sub>) receptors that has been approved by the US FDA for muscle spasticity.<sup>18</sup> In a recent meta-analysis of the results of anticraving effects of AUD from 12 randomized clinical trials, baclofen has been found to have good effect on abstinence rates when using intention-to-treat analysis, but no difference effects in heavy drinking days and craving score in patients on baclofen compared to those on placebo, suggesting that substantial heterogeneity exists in effect sizes across each analysis.<sup>40</sup> The investigators are still doing additional testing and review in the United States and Europe to clarify mixed results in small trials.<sup>18</sup>

## 6 | PUTATIVE MECHANISMS OF ACTION IMPLICATED IN DRUGS WITH ANTICRAVING BENEFITS FOR TREATING PATIENTS WITH AUD

The mechanisms of action of the above-listed anticraving drugs in treating AUD patients have captured fascination and imagination of many investigators in the field. The readers are advised to refer to original publications for more detailed explanations. Sampled points of explanations are described briefly.

### 6.1 | Opioid modulation

Opioids are referred to products that are extracted from plants or synthesized compounds (e.g., heroin, morphine, and oxycodone), and endogenous ligands include endomorphin, endorphin, enkephalins

(Leu and Met), and dynorphin.<sup>41,42</sup> Through three subtypes— $\mu$  (mu),  $\delta$  (delta), and  $\kappa$  (kappa)—of G protein-coupled opioid receptors, opioids produce inhibitory effects on downstream neurons when activated by endogenous ligands or synthetic receptor agonists.<sup>42,43</sup> The binding affinity of those endogenous ligands depends on different receptor subtypes.<sup>42</sup>

Many studies showed that opioid antagonists acting either at all opioid receptor subtypes or only at specific subtypes suppress alcohol drinking.<sup>44,45</sup> A complete inactivation (i.e., knockout) of the  $\mu$ -opioid receptor blocks alcohol self-administration in mice.<sup>46</sup> Naltrexone, a selective mainly  $\mu$  opioid antagonist and  $\kappa$  opioid antagonist to a lesser extent, was originally licensed by US FDA for treating patients with opioid overdose (www.fda.org). Later, it was also applied to treat AUD patients,<sup>47</sup> because animal studies showed that like opioid, alcohol can activate the endogenous opioid system.<sup>48</sup>

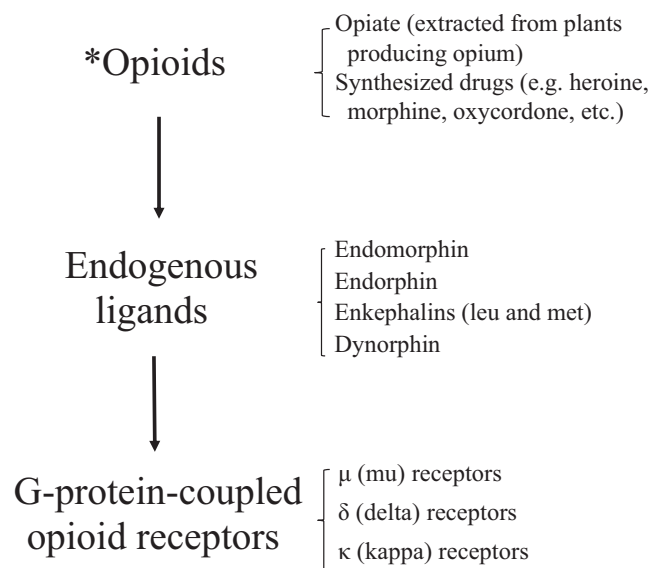
In translating this study finding,<sup>48</sup> an individual who receives naltrexone, cannot experience any extra euphoric effect if he/she takes opioids or drinks alcohol because some important portion of opioid receptors of the brain is blocked by naltrexone. Even though naltrexone blocks away the intense “high” from opioids or alcohol, it does not prevent good feelings that come from other naturally pleasurable activities. The individual still has other natural opioid receptors to bind, for example, endorphins from exercise. Figure 1 is a schematic illustration of how alcohol acts on endogenous opioid system.

As a peptide, opioid can stimulate inhibitory GABA neurotransmitter of interneuron in ventral tegmental area (VTA or area of Tsai, or A10), resulting in acting on A10 DA neurons. Eventually, DA is transmitted through DA mesolimbic tract to terminate in nucleus accumbens (NAc) as DA projection terminal fibers to have reward expressed.<sup>44,45</sup> Besides the afore-mentioned DA depending pathway, opioid or alcohol can directly interact on DA projection terminal fibers in NAc to express reward.<sup>45</sup> Taken together, naltrexone as an opioid antagonist, can block opioid actions through both DA dependent and DA independent pathways to produce anticraving benefit. More detailed description is as followed in subtitle 6.2 of this article.

### 6.2 | Dopamine neurotransmission

The reward system is transmitted through dopamine mesolimbic neurotransmission, from DA neurons originated from A10 of the midbrain, and terminated in DA projection terminal fibers in NAc.<sup>3</sup> The opioid peptide has been thought to be always co-localized and co-transmitted with DA neurotransmission in the brain. Opioid modulation action must be through activating DA system.<sup>49–51</sup>

DA is released in NAc, after alcohol or drug intake.<sup>51</sup> But previous study finding also suggests that DA independent opioid reward is possibly observed in opioid-naive states, but not in opioid-dependent states.<sup>52</sup> A recent study has further shown that the self-stimulation response of the brain is increased by stimulants but reduced by morphine,<sup>53</sup> suggesting that opioid dependence may change the GABA neurons from inhibitory to excitatory function, resulting in disappearance of DA independent opioid reward pathway.<sup>42</sup> These



**FIGURE 1** Schematic illustration depicting how alcohol\* acts on endogenous opioid system. Originally, the word “opioids” is a term denoting synthetic narcotics resembling opiates but increasingly used to refer to both opiates (produced from opium) and synthetic narcotics

study findings confirm that DA neurotransmission may not always be required for opioid reward responses in AUD patients.<sup>54–56</sup>

The mechanisms by which most of the addictive substances, except for alcohol, activated mesolimbic DA systems have been described to involve specific “receptors” for these addictive substances on the DA neurons of the VTA which project to the NAc, or on the projection terminal fibers of the DA neurons in NAc.<sup>51</sup> But the current work with alcohol indicates an indirect mechanism which involves the inhibition of GABA function in a particular area of brain.<sup>51</sup> This maybe the reason why none of existing anticraving drugs is based on DA hypothesis.<sup>47</sup> The clinical pharmaceutical pictures of anticraving drugs are differing from those in antipsychotic and antiparkinsonian drugs that are all based on DA hypothesis<sup>57</sup> and DA neurobiology,<sup>58</sup> respectively.

Alcohol activates opioid in the dopaminergic circuit of the reward indirectly, and stimulates the release of endogenous opioid peptides possibly at NAc directly.

### 6.3 | GABA neurotransmission

As stated in previous subtitle 6.2, DA transmission per se has not found to have any receptor to be activated by alcohol. The investigators have concentrated on studying two brain major neurotransmission systems—inhibitory GABA and excitatory glutamate neurotransmission systems—which have brought us much closer to identify the main pathways for the addicting characteristics of alcohol.<sup>51</sup>

After the discovery of benzodiazepines (BZDs), the studies on behavioral similarity of alcohol, BZDs, and GABA<sub>A</sub> have been increased.<sup>51,59</sup> Alcohol (or meprobamate, or barbiturate) does not compete with the BZDs for activating chloride ion channel, because

they do so on different loci although they act on the same receptor (BZD-GABA-chloride ionophore receptor complex).<sup>3</sup> That is why its effects, in joint administration, are enhanced, as they open up the channel in excess. Therefore, alcohol acts easily through endogenous GABA<sub>A</sub>, which is regulated by neuroactive steroids. Those neuroactive steroids are potential key modulators in developing alcohol dependence by acting directly at GABA<sub>A</sub> receptors.<sup>51,60</sup>

### 6.4 | Serotonin neurotransmission

Craving is mainly characterized by obsessional thoughts about drugs, causing compulsive drug-seeking and drug-taking behavior, therefore, the involvement of brain serotonin in the mechanisms of craving has been proposed.<sup>61</sup> Furthermore, the use of a selective serotonin 5-HT<sub>3</sub> antagonist (ondansetron) for patients with early-onset AUD has been investigated with good results of anticraving benefit.<sup>29</sup> The enthusiasm of using serotonergic antidepressants to treat AUD patients came alive<sup>62</sup> because the link between serotonin depletion, impulsivity, and alcohol drinking behavior has been observed in rats and humans.<sup>63,64</sup> But the neurobiology of serotonin involvement in anticraving efficacy is not yet clarified.

Antidepressants have been commonly used in all substance abusers due to the potential effect on some underlying mechanisms involved in substance use disorders and to treat comorbid depression. A meta-analysis was carried out on the studies of the efficacy of antidepressant drugs from randomized, double-blind, controlled trials in patients with substance use disorders (alcohol, cocaine, nicotine, and opioid), with and without comorbid depression.<sup>30</sup> The study result showed that the use of all (including serotonergic) antidepressants do not show any anticraving benefit in AUD patients without depression.<sup>30</sup> But a study showed that the G protein-activated inwardly rectifying potassium (GIRK) channel currents induced by alcohol can be inhibited by sertraline but not by intracellularly applied sertraline, suggesting that GIRK channel inhibition may reveal a novel characteristic of the commonly used antidepressants, particularly sertraline.<sup>65</sup> Future attention on serotonin neurotransmission on the role of anticraving benefit should be paid in this aspect.

As stated previously, the recent APA practice guideline does not mention any endorsement for the use of any 5-HT<sub>3</sub> antagonist for anticraving use against alcohol dinking.<sup>4</sup> (In fact, ondansetron is only available in intramuscular injection formulary for antiemetic use for cancer patients receiving chemotherapy.) Meanwhile, the APA guideline also does not recommend or suggest for any antidepressant medications for treating AUD patients unless a comorbid disorder exists for which an antidepressant is an indicated treatment.<sup>4</sup>

### 6.5 | Glutamate neurotransmission

Being an excitatory neurotransmitter, glutamate is an agonist of kainate, NMDA, and AMPA receptors.<sup>3</sup> DA transmission system receives excitatory glutamate input at VTA from peduncular pontine tegmentum (PPT) and lateral dorsal tegmentum (LDT) of the amygdala, and at NAc from the cortex of the brain.<sup>44,45</sup>



The present data indicate that acamprosate has an extremely weak antagonism of NMDA-receptors, but its principal anti-drinking biochemical effect is thought to be from modulating the expression of NMDA-receptor subunits in specific brain region that is shared with the well-established NMDA-antagonists memantine and MK-801.<sup>66</sup> But the investigators suggest the growing importance of NMDA-receptor plasticity in the AUD research.<sup>66</sup>

### 6.5.1 | Blockage of GIRK channel

As a postsynaptic transduction system of glutamate receptor, GIRK channel has four subunits.<sup>66,68</sup> Results of cloning study showed that GIRK1, GIRK2, and GIRK3 are distributed in various brain regions (cerebral cortex, amygdala, hippocampus, VTA, locus coeruleus, cerebellum), and GIRK4 is expressed mainly in the heart.<sup>66–68</sup>

Investigators found that induced GIRK current is inhibited by ifenprodil using *Xenopus* oocyte expression assays.<sup>66,69</sup> GIRK2 knockout mice showed reduced alcohol-induced conditioned taste aversion and conditioned place preference.<sup>70</sup> Weaver mutant mice which are missense mutation in channel pore in GIRK2 subunit have been found to have reduced antinociceptive effects of alcohol.<sup>71</sup> These studies suggest that ifenprodil is effective for blocking alcohol-activated GIRK channels.

A recent study showed that combination of pretreated with ifenprodil and cyproheptadine (antagonist of 5-HT<sub>2</sub> receptor) in the mice inhibits alcohol intake and decreases alcohol preference compared to the mice pretreated with saline.<sup>72</sup> Furthermore, they also showed the combination of cyproheptadine and prazosin (antagonist of  $\alpha$ -1 adrenergic receptor) also decreases alcohol preference, but separation of administration of these drugs has not found to be effective for alcohol preference. In addition, the antagonist studies show that concurrently activated NMDA and GABA channels each tend to limit the responses of the other.<sup>72</sup> These studies suggest that GIRK channel may have a key molecule in alcohol dependence and ifenprodil is one of a candidate drug in medical treatment.

## 6.6 | Summary of mechanisms of action in anticraving drugs

### 6.6.1 | Lists of anticraving drugs

Table 1 lists possible mechanisms implicated for anticraving drugs in treating AUD patients. Expansion of the list is expected if the research in the field is intensified, and the revision is also expected if more new research evidences are accumulated, especially for those anticraving drugs that have been in use to treat nonalcohol other substance use disorders.<sup>73,74</sup>

### 6.6.2 | Circuitry of brain reward pathway

Nestler<sup>44</sup> as well as Gilpin and Koob<sup>45</sup> did schematic presentations for brain reward circuitry. Readers should refer to the original graphs for more detailed descriptions. Here, the contents are paraphrased.

**TABLE 1** Possible mechanisms implicated for anticraving actions in treating alcohol use disorder patients

Mechanism of action of anticraving drugs	Applicable drugs
Opioid modulation	Naltrexone, Nalmefene
Dopamine neurotransmission	Naltrexone, Nalmefene
Serotonin neurotransmission	Ondansetron
GABA neurotransmission	Gabapentin
Glutamate neurotransmission	Acamprosate
Blockage of GIRK channel	Ifenprodil

GABA,  $\gamma$ -aminobutyric acid; GIRK channel, G protein-activated inwardly rectifying potassium channel.

### DA depending brain reward pathway

From VTA to NAc, DA mesolimbic tract is the main brain reward pathway in carrying alcohol craving/anticraving message. VTA can receive both inhibitory GABA<sub>A</sub> transmission as interneuron as well as excitatory glutamate transmission from amygdala (PPT and LDT). The entry points for alcohol and opioid to act are at GABA<sub>A</sub> neurons. Alcohol can possibly activate DA by stimulating the release of opioid peptide at VTA.<sup>44,45</sup>

### DA independent brain reward

Alcohol and opioid can directly interact on DA projection terminal fibers at NAc to express reward. NAc also receives glutamate input from the brain cortex. Alcohol can also possibly activate DA by stimulating the release of opioid peptide at NAc.<sup>44,45</sup>

## 7 | CLINICAL PRACTICE OF PRESCRIBING ANTICRAVING DRUGS FOR TREATING PATIENTS WITH AUD

### 7.1 | Treating AUD patients with anticraving drugs is gratifying

Comparing to only limited armamentarium in treating AUD patients in 1991,<sup>1</sup> the author is amazed in writing this current review that several anticraving drugs are available to stop patients' craving against drinking. My 20-year clinical experiences in prescribing anticraving drugs have been rewarding.

The author used to prescribe disulfiram (Antabuse<sup>®</sup>) before the advent of naltrexone in the United States in 1980s and early 1990s in the setting of alcoholism treatment program.<sup>75</sup> The disulfiram-medicated patients still have urge to drink alcohol, but they are deterred from drinking because of their fear of developing DER.<sup>1,3</sup> As the stipulation of her employment, a 45-year-old female custodian patient at a local elementary school needed to take disulfiram in front of staff in the office of the school principal's office every morning weekdays. She was cut off the chance of alcohol drinking weekdays and the weekend due to her taking disulfiram in the morning weekdays. She did not want to take chance to drink any alcohol because of her fear of having DER. She believed that some of disulfiram was still in her body during



the weekend. She was kept to be sober for at least 3 years with disulfiram.

Then, the author stopped prescribing disulfiram in late 1990s when naltrexone (ReVia<sup>®</sup> or Vivitrol<sup>®</sup>) became available. I still remember vividly that a naltrexone-medicated patient of about 50 years of age, a university professor in the United States, could stop all his alcohol drinking completely for the first time in his 6-month outpatient treatment at my regular psychiatric clinic after the use of naltrexone. He told me and he could forget about alcohol drinking completely, and started to prepare and update his teaching slides of his lecture files for his class at a medical school. In Taiwan, naltrexone had been once unavailable till 2 years ago because only limited prescriptions made the pharmaceutical company to decide not to supply the drug for about 5 years. But naltrexone is currently available (M. C. Huang, personal communication, 2018).

The author has not had the chance to prescribe acamprosate (Campral<sup>®</sup>). I did prescribe only a couple of patients with gabapentin (Neurontin<sup>®</sup>) for anticraving use. The patients mentioned sedation and paresthesia as the side effects. They also complained of the cost due to off-label use.

The author has been offering patients to prescribe topiramate (Topamax<sup>®</sup>)<sup>76</sup> for off-label use to curb their alcohol drinking if they so desire. The patients have to pay the extra expense of this drug outside of the medication coverage from Taiwan National Insurance Institute due to the lack of official indication in Taiwan. Instead of the dosage used in clinical drug trial of 300 mg/d,<sup>22–24</sup> the dosage of topiramate I have prescribed is 100 mg/d for anticraving therapy.<sup>76</sup> But I start with 50 mg for the first night at bedtime. Then, the patient takes 100 mg/d at bedtime from the second day on. I may reduce the dosage to 75 mg nightly if the patient complains of

tingling sensation of the arms. I have found that the use of topiramate is more convenient than that of naltrexone because patients' liver conditions are not a concern. The patient can start to take topiramate on the first day while they are receiving outpatient detoxification with the use of a BZD.<sup>3</sup> The patient and his/her family have been warned about the memory problems from using topiramate, BZD, and alcohol.<sup>3</sup> All my topiramate medicated-patients are seen weekly until they are completely sober. Then, they are given monthly prescription for topiramate, which can be combined with any concurrent antidepressants without any concerns of drug-drug interaction.<sup>76–78</sup> Usually, most of all my patients welcome the use of topiramate because of its superior anticraving benefit to naltrexone.<sup>79</sup> What's more, topiramate has good profile in keep the body weight under control.<sup>3,76,80</sup>

## 7.2 | Anticraving drugs can be given at regular outpatient clinics

All the anticraving drugs can be prescribed in regular psychiatric clinic. The prescriptions of anticraving drugs are prescribed in the clinics of family medicine clinics.<sup>10,81</sup> Most of anticraving drugs are available in hospital formulae for indications of other medical conditions. For example, ifenprodil was developed in France and was released from 1979 in Japan as a cerebral circulation/metabolism ameliorator. Original drug is Cerocral that is from Sanofi, France, is sold in Japan. Ifenprodil tartrate is available in France, Korea, Philippines, and Japan.

The urgent and immediate goal is to use an anticraving drug to reduce AUD patients' craving for alcohol. At this moment, various medications such as naltrexone, topiramate, and gabapentin in the

**TABLE 2** Representing anticraving drugs for patients with alcohol drinking disorder

Drug	Drug profile responsible for anticraving properties	Representing human anticraving studies	Other medical use besides anticraving therapy
Naltrexone <sup>a</sup>	A glutamate agonist, is derived from amino acid, taurine	Weinstein et al (2003) <sup>5</sup>	
Naltrexone <sup>a</sup>	A main $\mu$ and $\delta$ (lesser extent) opioid receptor antagonist	Volpicelli et al (1992) <sup>11</sup> O'Malley et al (1992) <sup>12</sup>	Opioid overdose
GHB <sup>b</sup>	A precursor to GABA, glutamate, and glycine	Addolorato et al (1996) <sup>14</sup>	Narcolepsy
Nalmefene <sup>b</sup>	A $\mu$ -opioid receptor antagonist & $\kappa$ -opioid partial agonist	Gual et al (2013) <sup>19</sup> van den Brink et al (2014) <sup>20</sup>	
Topiramate	An antagonist for kainate/AMPA, a subtype of the glutamate	Johnson et al (2003) <sup>22</sup> Johnson et al (2004) <sup>23</sup> Johnson et al (2007) <sup>24</sup>	Epilepsy Migraine Lennox-Gastaut syndrome
Gabapentin	A drug to facilitate GABA transmission	Furieri & Nakamura-Palacio (2007) <sup>27</sup> Mason et al (2014) <sup>28</sup>	Epilepsy Nerve pain
Ondansetron	A 5-HT <sub>3</sub> reuptake inhibitor	Johnson et al (2000) <sup>29</sup>	Antiemetic for cancer patients receiving chemotherapy
Ifenprodil	A GIRK channel inhibitor	Sagaya et al (2018) <sup>35</sup>	Dizziness in poststroke patients

The Arab numbers in superscripts denote the reference entries cited in the article.

AMPA receptors,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors; GABA, gamma-aminobutyric acid; GHB, gamma-hydroxybutyrate; GIRK channel, G protein-activated inwardly rectifying potassium channel.

<sup>a</sup>Approved by US Food and Drug Administration for anticraving indication in patients with alcohol use disorder.

<sup>b</sup>Approved by European Medicines Agency for anticraving indication in patients with alcohol use disorder.



United States, as well as ifenprodil in Japan, are readily available for clinicians to prescribe for those with AUD patients.

Table 2 lists representing anticraving drugs for treating AUD patients. This table is intended to familiarize clinicians with the available drugs for prescription. The more a clinician prescribes for the AUD patients, the more he or she learns about the benefit if the patients are kept sober from drinking.

## 8 | CONCLUSION

To re-state, the author is amazed at the availability of various anti-craving drugs being described in this review, compared to the drugs to treat AUD patients in 1991,<sup>1</sup> Thanks for all diligent researchers to develop all those drugs. But, we need to keep up with the work because all anticraving drugs as “a class of drugs” are still much less than what antipsychotic drugs or antidepressants exist on the market now.

Despite APA practice guideline “recommends” the use of acamprosate and naltrexone, and “suggests” the use of topiramate and gabapentin for AUD patients,<sup>4</sup> anticraving drugs are not well-known and are underused by clinicians. All those drugs mentioned here have ability to curb alcohol drinking to keep patients sober to perform proper societal roles and to be productive citizens. Therefore, we need to write more articles about anticraving drugs,<sup>82–84</sup> to educate clinicians and lay public to promote the awareness of the disease of AUD, treatment and the availability of anticraving drugs. In Japan, the concept of major depressive disorder was popularized as the “cold of the heart” (*kokoro no kaza*) in 1980s and 1990s, and this promotional language did help the sale of antidepressants.<sup>77,85,86</sup> Therefore, I think that those articles on anticraving drugs,<sup>82–84</sup> are important to promote the public awareness of AUD and the use of anticraving drugs in Japan.

Let me go to the epigraph, the opening quotation sentence before the introduction section of this article. To agree with Gryphon's sentiments is quite easy, but to understand the “adventure” of the anti-craving therapy clinically for AUD patients is essential to explain. The potential benefit of each drug described here in this article is viewed as far-outweighing the possible side effects of anticraving drugs or the harms of continued use of alcohol. Thus, let's be more adventurous to prescribe an anticraving drug for our next AUD patient!

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## CONFLICT OF INTEREST

The author declares no potential conflict in writing this review.

## DISCLAIMERS

The contents of this review contain information on off-label use of released licensed medications. The readers need to read package insert on dosage and side effects of each drug mentioned in this review before the prescribing them to patients.

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