NEUROBEHAVIOURAL BASIS FOR THE PHARMACOTHERAPY OF ALCOHOLISM: CURRENT AND FUTURE DIRECTIONS
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Abstract — Results from studies of pharmacotherapies for primary alcoholism are reviewed, including selective serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitors (e.g. fluoxetine), opiate antagonists (e.g. naltrexone) and dopamine agonists (e.g. bromocriptine). Because there is considerable co-morbidity between alcohol dependence, anxiety, and affective disorders, results from studies of medications used to treat these psychiatric disorders are also reviewed, including the 5-HT agonist buspirone and the noradrenergic agent desipramine. The neurobehavioural model of alcohol dependence implies that combinations of medications may lead to more effective treatment; thus, identifying subtypes of alcoholic patients will be important in determining which therapies or combinations of therapy will be most effective in treating alcohol dependence. For example, in an ongoing study, we are attempting to subtype an alcoholic population for treatment selection by measuring endogenous opioid activity. Because endogenous opioids are involved in analgesia, we exposed male and female subjects with alcoholism [some of whom had post-traumatic stress disorder (PTSD)] to cold-induced pain and measured their response before and after administration of naloxone or placebo. The naloxone injection reduced pain response. In addition, women who have PTSD are much more sensitive to stress, which may be related to levels of brain opioid activity.

INTRODUCTION
In recent years, a growing number of animal and human studies have increased our understanding of the neurochemical effects of alcohol (Litten and Allen, 1991; Jaffe et al., 1992; Kranzler and Anton, 1994). Progress has also been made in identifying brain structures and pathways involved in reward sensation (Robinson and Berridge, 1993; Erickson, 1996) and stress reduction (Volpicelli et al., 1986; Pohorecky, 1991; Koob, 1992), both of which play a critical role in initiating alcohol-seeking behaviour. In addition, animal models have been developed that allow researchers to test various hypotheses with regard to how pharmacologic agents might be used to alter neurochemistry and thereby reduce alcohol consumption (Froehlich and Li, 1991). Findings from these studies can predict drug efficacy in the treatment of alcoholism.

Hypothetical links exist between the neurochemical systems, the stress-reducing and reward-enhancing effects of alcohol, and the processes of sensitization and craving that lead to compulsive drinking. Within this hypothetical framework, the results of pharmacologic attempts to treat alcohol dependence are reviewed briefly herein. For example, a study currently underway at our Center for Drug and Alcohol Programs provides one example of how alcoholic populations are being studied to more clearly differentiate biological subtypes that might predict response to treatment. Patients’ response to naltrexone, an opiate antagonist, will be evaluated based on their response to pain and stress, which may be related to the level of endogenous opioid activity in the brain.

Much research is needed to expand our understanding of the effects of alcohol on neurochemical interactions. Nonetheless, knowledge gained to date can lead to meaningful hypotheses and neurobehavioural models that allow us to understand better how alcoholism develops and how combinations of pharmacologic and psychosocial therapies can be used to treat this prevalent disorder.

NEUROBEHAVIOURAL MODEL OF ALCOHOL DEPENDENCE
The primary symptom of alcohol dependence is loss of control over drinking (Rinaldi et al., 1988;
Morse and Flavin, 1992). According to the Diagnostic and Statistical Manual for Mental Disorders, 4th edition, loss of control is behaviourally defined as initiating drinking despite obvious negative consequences, or drinking more than is intended (Task Force on DSM-IV, 1994). How an individual progresses from the use of alcohol for reward sensation and stress reduction, which are experiences common to all people who consume alcohol, to the compulsive use of alcohol, which affects only certain individuals, is a crucial question. A neurobehavioural model (Fig. 1) offers one approach to conceptualizing the development of alcohol dependence.

**Reward sensation**

The term ‘reward’ refers to the feeling of euphoria or the ‘high’ produced by addictive drugs. Alcohol reward depends on an interaction of dopamine and opioid peptides (Wise and Rompre, 1989; Koob, 1992). The reward sensation stimulated by alcohol consumption involves the activity of endorphins, enkephalins, dopamine, and, perhaps, serotonin (van Ree, 1979; McBride et al., 1990; Koob, 1992; Robinson and Berridge, 1993; Weiss et al., 1993; Kranzler and Anton, 1994). The positive reinforcement associated with reward has long been thought to play a role in the development of compulsive drinking, but stress can also lead to compulsive drinking (Volpicelli et al., 1990).

**Stress reduction**

The role of stress in the development of compulsive drinking is supported by studies that indicate that anxiety and depression are the two most common co-morbid conditions found in alcoholic patients (Regier et al., 1990; Anthenelli and Schuckit, 1993). Drugs that affect the neurotransmitters noradrenaline (norepinephrine) and 5-HT have been shown to alleviate the symptoms of anxiety and depression; thus, these neurotransmitters appear to play a prominent role in these conditions (van Praag et al., 1987; Richardson, 1991). Agents that affect noradrenaline or 5-HT activity are being used to treat alcoholic patients who have co-morbid conditions (Naranjo and Bremner, 1992; Anton, 1995; Brady and Roberts, 1995).

Alcohol is perhaps more potent than effective anxiolytic agents in the enhancement of γ-amino butyric acid (GABA)-mediated neuronal inhibitory activity and affects norepinephrine activity as well. A growing body of literature suggests that these neurotransmitters are particularly important in the type of stress associated with certain anxiety disorders (Charney and Heninger, 1986) and post-traumatic stress disorder (PTSD).

Stress may cause predisposed individuals who have clinically significant anxiety or depressive disorders to use alcohol to ‘self-medicate’. Such individuals also may have an abnormality in their reward-sensation system, which puts them at

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Fig. 1. Neurobehavioural model of alcohol dependence. GABA = γ-aminobutyric acid
unusual risk for the development of alcohol dependence.

Sensitization

'Sensitization' refers to the process by which a person begins to increase the use of alcohol or to more strongly experience the craving for, or the anticipation of, alcohol's effects over time. Robinson and Berridge (1993) made a particularly strong argument for dopamine's role in the development of sensitization. Sensitization could play a crucial role in the progression from using alcohol for stress reduction or reward sensation to using it compulsively. For example, sensitization could lead to generalization of drinking cues from the ingestion of alcohol itself to environmental stimuli associated with alcohol intake or to feeling states (dysphoria, anxiety) normally relieved by the ingestion of alcohol (Cooney et al., 1984; Monti et al., 1993). Sensitization could also account for the 'priming effect' described as the 'one drink—one drunk' phenomenon for any alcohol consumption as scientifically described (Hodgson et al., 1979) and operationalized in the tenets of Alcoholics Anonymous. In essence, sensitization underlies the lost control over drinking that is central to the illness of alcohol dependence. For instance, the alcoholic patient who has achieved long-time abstinence may experience a slip or relapse after a major life stress leading to anxiety or depression, which is the sensitized stimulus to alcohol consumption. During this period, craving increases and the patient may finally succumb to drinking. Another example would be the alcoholic patient in early recovery who goes to a party with old drinking buddies. The sensitized cues of friends, familiar places, and a favourite beverage may stimulate intense craving, and that first drink sensitizes this individual even more, thus an alcoholic slip or relapse occurs. Desensitization is a crucial component of the recovery process and integral to relapse prevention therapy. Its neurobiologic substrate is also a likely place to target pharmacotherapy.

Craving and obsessional thinking

'Craving' and 'obsessional thinking' are additional aspects of compulsive alcohol consumption (Modell et al., 1992; Anton et al., 1995). Craving refers to a state of mind, or perhaps a drive, that is subcortical (i.e. it originates from the area of the brain below the cerebral cortex, where concepts and words are formed; thus, it is not easily defined or quantified) (Anton, 1995). Obsessional thinking refers to a mental state in which alcoholic patients, especially during the initial stages of treatment, have a constant internal dialogue about whether to drink or remain abstinent. The drive to use alcohol and the patient's attempts to resist that drive are similar to the phenomena experienced by patients with obsessive-compulsive disorder (OCD). As indicated by the successful use of serotonergic drugs to treat OCD (Goodman et al., 1990), 5-HT may play a major role in obsessional thinking about, or craving for, alcohol (for review, see Kranzler and Anton, 1994).

Neurochemical interactions

In the neurobehavioural model of alcohol dependence (Fig. 1), the arrows point both ways, which implies that neurotransmitters influence each other. Dopamine might modulate reward sensation and stress reduction (Di Chiara and Imperato, 1988; Weiss et al., 1993; Kranzler and Anton, 1994); conversely, noradrenaline, GABA, endorphin, enkephalin, and dopamine all might modulate sensitization (Robinson and Berridge, 1993; Erickson, 1996).

Interactions between the serotoninergic and dopaminergic systems might play an important role in the reinforcing effects of alcohol (Kranzler and Anton, 1994), since several serotoninergic drugs that reduce alcohol consumption in animals and humans affect the dopamine system (Kranzler and Anton, 1994; Ugedo et al., 1987; Wozniak et al., 1990).

Implications for treatment of alcohol dependence

The neurobehavioural model implies that combinations of medications and psychological approaches may lead ultimately to more effective treatment (Fig. 1). For example, a serotoninergic agent that decreases obsessional thinking or craving may be combined with a dopaminergic agent that suppresses sensitization or with an opiate antagonist that suppresses reward sensation. Medications may decrease subcortical brain drive mechanisms, while psychosocial approaches may increase cerebral-cortical inhibitory control mechanisms. The concomitant use of both types of treatment might produce an additive effect and
achieve greater control over alcohol consumption (Anton, 1995). Subtyping alcoholic patients will be of crucial importance in any attempt to determine which therapies alone, or in combination, might be most effective in a given patient (Project MATCH Research Group, 1993; Kranzler and Anton, 1994).

**MEDICATIONS FOR THE TREATMENT OF PRIMARY ALCOHOLISM**

Table 1 lists the various pharmacologic agents that have been studied for the treatment of primary alcoholism (Meyer, 1989; Kranzler and Orrok, 1989; Litten and Allen, 1991; Naranjo and Sellers, 1992; Kranzler and Anton, 1994; Anton, 1995). In all of these studies, the goal was to demonstrate that using pharmacologic agents to alter brain chemistry, sometimes combined with relapse prevention therapy, reduces consumption of, and/or maintains abstinence from, alcohol. Hypothetically, this change in neurochemistry should decrease the reward sensation associated with alcohol, increase stress tolerance, or both, so that the individual would become desensitized to alcohol-related cues and would resist or unlearn the behavioural drive to consume alcohol.

In general, the selective serotonin reuptake inhibitors (SSRIs) have had only mild to no effect in the treatment of alcohol dependence (Naranjo and Bremner, 1992; Gorelick and Paredes, 1992; Kranzler et al., 1995). However, fluoxetine has been shown to decrease alcohol intake in early stage problem drinkers (Naranjo et al., 1990).

While the SSRIs non-specifically increase 5-HT in sensitive neuronal synapses, other medications work more specifically on subtypes of 5-HT receptors. Examples of more specific serotoninergic drugs are ritanserin and ondansetron. Ritanserin, which is primarily a 5-HT2 antagonist, although shown in preliminary studies to be of potential use in alcoholism, was not found effective in a randomized, double-blind multi-site study (Greb, 1995; Janssen Pharmaceuticals, data on file). Ondansetron, however, which is a 5-HT3 agonist, was reported to be effective in reducing drinking in a group of problem drinkers who likely had early or mild alcohol dependence (Sellers et al., 1994).

The mechanism of action of the serotoninergic agents has not yet been clarified; one hypothesis suggests that they operate by decreasing general appetitive behaviours (Naranjo and Sellers, 1989), although other recent data suggest an interactive role of some of these agents and other crucial neurotransmitter systems such as dopamine (Ugedo et al., 1987; Wozniak et al., 1990).

The opiate antagonist naltrexone has shown a strong effect in the treatment of primary alcohol-
Table 2. Medications studied for the treatment of patients with co-morbid alcoholism and psychiatric disorders

<table>
<thead>
<tr>
<th>Class</th>
<th>Psychiatric disorder</th>
<th>Study design</th>
<th>Efficacy</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotoninergics</td>
<td></td>
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<tr>
<td><em>Buspirone</em></td>
<td>Generalized anxiety</td>
<td>Double blind</td>
<td>−/+</td>
<td>Malcolm et al. (1992); Kranzler et al. (1994)</td>
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<tr>
<td><em>Fluoxetine</em></td>
<td>Depression</td>
<td>Open</td>
<td>Mild +</td>
<td>Cornelius et al. (1993)</td>
</tr>
<tr>
<td><em>Fluoxetine</em></td>
<td>Depression</td>
<td>Double blind</td>
<td>Ongoing</td>
<td></td>
</tr>
<tr>
<td><em>Sertraline</em></td>
<td>Depression</td>
<td>Double blind</td>
<td>Ongoing</td>
<td></td>
</tr>
<tr>
<td><em>Sertraline</em></td>
<td>PTSD†</td>
<td>Open</td>
<td>Mild +</td>
<td>Brady et al. (1995)</td>
</tr>
<tr>
<td>Noradrenergics</td>
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<tr>
<td><em>Desipramine</em></td>
<td>Depression</td>
<td>Double blind</td>
<td>Mild +</td>
<td>Mason and Koegis (1991)</td>
</tr>
<tr>
<td><em>Imipramine</em></td>
<td>Depression</td>
<td>Open</td>
<td>Mild +</td>
<td>Nunes et al. (1993)</td>
</tr>
<tr>
<td><em>Imipramine</em></td>
<td>Panic</td>
<td>Double blind</td>
<td>Ongoing</td>
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<tr>
<td>Mood stabilizers</td>
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<tr>
<td><em>Lithium</em></td>
<td>Depression</td>
<td>Double blind†</td>
<td>—</td>
<td>Dorus et al. (1989)</td>
</tr>
<tr>
<td><em>Valproate</em></td>
<td>Bipolar affective</td>
<td>Open</td>
<td>Mild +</td>
<td>Brady et al. (1995)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>Double blind</td>
<td>Ongoing</td>
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*Commercially available.
†Post-traumatic stress disorder.
‡Multisite study.

isom (Volpicelli et al., 1992; O'Malley et al., 1992; see also O'Malley, 1996). By blocking opioid receptor activity, naltrexone is believed to block reinforcement and reduce excessive drinking (Volpicelli et al., 1992). The groups of Volpicelli and O'Malley showed that naltrexone reduced rates of relapse into heavy drinking by ~50% in alcohol-dependent subjects over a 12-week period; all patients received psychosocial treatment. Nalmefene, another opiate antagonist, has also been found to reduce alcohol consumption and relapse into heavy drinking (Mason et al., 1994).

The antimanic medication lithium has not been found to be effective in patients who have either primary alcoholism or alcoholism with a history of depression, although this lack of efficacy may be related to a low level of compliance with treatment (Dorus et al., 1989; Lejoyeux and Adès, 1993).

Bromocriptine, a dopamine agonist, is one of the few drugs studied that works directly on the dopamine system. A relatively small study in Scandinavia found that it had a mild effect on alcohol consumption (Borg, 1983). Alcoholics who received bromocriptine reported a reduction in craving and alcohol use over a 6-month period.

MEDICATIONS TO TREAT CO-MORBID ALCOHOLISM AND PSYCHIATRIC DISORDERS

Considerable co-morbidity exists between alcohol dependence and anxiety and affective disorders (Regier et al., 1990; Kessler et al., 1994). Table 2 lists pharmacologic agents that have been used to treat patients who had co-morbid conditions. Buspirone, a 5-HT1A agonist, has been shown to be effective in the treatment of generalized anxiety and is approved by the Food and Drug Administration for that use in the USA. Our study in a Veterans Affairs population (Malcolm et al., 1992) found a complete lack of efficacy in anxious alcoholic patients; however, another study showed buspirone to be effective in reducing alcohol consumption among anxious patients who were mild to moderate abusers of alcohol and who also received coping skills or cognitive behavioural therapy (Kranzler et al., 1994). This provides an example of how a drug may work differentially, depending on the population selected and the type of psychosocial therapy provided with the medication.

Preliminary studies suggest that fluoxetine, an SSRI, may reduce drinking in alcoholic patients...
with major depression (Cornelius et al., 1993). Preliminary results in a study of patients with PTSD suggest that the SSRI sertraline reduces alcohol intake and symptoms of PTSD (Brady et al., 1995).

A relatively small study of desipramine, a noradrenaline uptake blocking tricyclic antidepressant, showed that it decreased both depression and alcohol consumption in depressed alcoholic patients (Mason and Kocsis, 1991). The reduction in alcohol consumption was only mild, but desipramine was effective in alleviating depression. Most importantly, this study showed that a tricyclic antidepressant can be used safely to treat depressed alcoholic patients but that plasma levels of the antidepressant may need to be monitored to ensure efficacy.

In an open study of 85 patients with dual diagnoses of alcohol dependence and an affective disorder, imipramine, a tricyclic antidepressant, was shown to have a small effect on alcohol consumption. Sixty subjects received a trial of imipramine (mean dosage = 263 mg/day, SD = 77, range = 150–500; mean blood level = 368 ng/ml, SD = 264, range = 46–928). Twenty-seven (45%) of the patients improved substantially in mood and drinking behaviour, 18 (30%) were abstinent from alcohol, and nine (15%) continued to drink but at a lower level (Nunes et al., 1993).

In summary, the SSRIs have not consistently demonstrated a high level of efficacy in the treatment of alcohol dependence, and none has been as effective as opiate blockers, particularly naltrexone. In some patients with dual diagnoses, studies have shown that buspirone and fluoxetine used to treat the primary psychiatric disorder may be effective in the treatment of alcohol dependence, particularly as an adjunct to other therapeutic approaches, such as cognitive behavioural therapy.

Differences in study populations may affect the interpretation of outcomes. For example, most of the work done in Toronto at the Addiction Research Foundation (Naranjo and Bremner, 1992) has been with subjects described as ‘heavy drinkers’, some of whom probably would meet the criteria for mild alcohol dependence but generally are not seeking treatment and do not necessarily have the motivation to stop drinking. These subjects were selected for this study design, so that researchers could evaluate whether the medication by itself would reduce drinking. Conversely, other studies that include alcohol-dependent subjects involve highly motivated people who are seeking treatment to stop or at least reduce their drinking.

**SUBTYPING ALCOHOLIC PATIENTS**

To identify alcoholic patients who require specific treatment, there is a need to identify alcoholic patients with additional psychiatric diagnoses. In addition, individuals who have primary alcoholism may be subtyped by their differential responses to particular biological challenges. Those responses might be used to match specific pharmacologic treatments for these individuals.

For example, m-chlorophenylpiperazine (mCPP), a 5-HT receptor agonist, can be administered to alcoholic and control subjects to compare biochemical differences by measuring their neuroendocrine responses in terms of prolactin or cortisol concentration in plasma and/or by asking subjects if they feel intoxicated.

Several studies have shown that administration of mCPP is more pleasurable or intoxicating for alcoholic subjects than for control subjects (Krystal et al., 1994). This suggests an abnormality in the serotonergic systems of a subtype of alcoholic patients. Those subjects might be expected to respond differently to treatment with serotonergic agents, although this has not yet been reported.

**RESPONSE TO COLD-STRESS PAIN: AN ONGOING STUDY**

At our study centre, we are attempting to assess endogenous opioid activity in a group of alcohol-dependent subjects prior to randomization into a double-blind, placebo-controlled trial of naltrexone plus cognitive behavioural therapy. So that endogenous opioid activity in the brain could be evaluated without performing invasive procedures (i.e. intracranial tissue biopsy or lumbar puncture for cerebrospinal fluid), we are examining how the subjects respond to pain induced by an external stressor, i.e. cold water. Knowing that endogenous opioids are involved with analgesia, we hypothesized that opioid system activity could be measured by exposing alcoholic subjects to a painful stressor and measuring their responses...
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It had been previously shown that alcohol or the expectancy of drinking alcohol increases pain tolerance in a group of heavy drinking and alcoholic subjects. It was hypothesized that the opioid system may be involved with this response and that naloxone would alter this effect (Cutter and O'Farrell, 1987).

SUBJECTS AND METHODS

In our trial, study subjects included 29 men without PTSD, four women with PTSD, and 10 women without PTSD. Subjects were required to remain abstinent from alcohol for 5 days before the study. Subjects immersed a hand in ice-cold water (~0–2°C) for up to 1 min. Every 10 s, subjects rated their pain on a 10-point scale, for a maximum pain score of 60. The following day, subjects received an intravenous injection of either naloxone (10 mg) or saline solution in a counterbalanced fashion and received a placebo-alcohol drink (for ethical reasons, the subjects did not receive alcohol, but they believed they were being given alcohol). After each injection and placebo drink, subjects repeated the cold-water immersion and pain-rating procedure.

Results

As shown in Fig. 2, the baseline results show a very mild, non-significant gender effect, with the exception of the four women with PTSD, who exhibited much less pain tolerance. It has been hypothesized that people who have PTSD might have an endogenous opioid deficiency and may therefore drink alcohol to increase endogenous opioid tone (van der Kolk et al., 1989). Furthermore, women who have PTSD experience a high rate of alcoholism as well as other substance abuse (Burnam et al., 1988; Swett et al., 1991). Thus, this preliminary finding, even with a small number of subjects, suggests that women who have PTSD may be more sensitive to stress (i.e. may actually have a lower baseline level of opioid activity).

Figure 3 shows the combined pain data for men and women without PTSD as a response to alcohol expectancy and placebo versus naloxone injection. Contrary to published data, alcohol expectancy did not significantly reduce the level of pain experienced in our group of alcohol-dependent subjects. However, counter to our expectation, when these subjects received the opiate antagonist naloxone before alcohol expectancy, they actually had much greater pain tolerance ($P = 0.002$), even though this agent blocks opioid activity.

The main reason for conducting the study, however, was to attempt to subtype an alcoholic population; our initial findings lend support to this possibility. Approximately one-half of the subjects enrolled in our ongoing study experienced a pain reduction (stress-dampening) effect when naloxone was combined with alcohol expectancy; the other half did not experience this effect. During treatment, one half of these subjects will receive naltrexone, and the other half will receive placebo plus cognitive behavioural therapy for 12 weeks. We intend to evaluate whether the subjects who experienced the initial pain-dampening effect
of naloxone have a greater therapeutic response to naltrexone. If there is a strong correlation between the effects of naloxone and naltrexone in pain dampening, this paradigm could be used to predict an individual's response to naltrexone. As such, this could be one approach that might enable researchers to define biological specificity in drug selection. In addition, data such as these might help to define basic mechanisms that may differ between alcoholic and control subjects or between subgroups of alcoholic patients.

**DIRECTIONS FOR FUTURE RESEARCH**

Future efforts appear best targeted in several different areas. In the preclinical area, we need a better understanding of which opioid receptor subtypes (mu, delta, or kappa) are most important in the reinforcing effects of alcohol. Dopamine agonists and antagonists will require testing for their ability to inhibit the development of sensitization and to reduce alcohol intake. We also need to accelerate basic studies that attempt to provide animal models of alcohol consumption and that examine the interrelations of the various neurochemical systems on reward and sensitization.

Clinically, the development of paradigms that predict the utility of pharmacologic agents prior to starting treatment protocols will be critical, because of the time and cost considerations in conducting treatment trials. Finally, we need to define better the role of psychosocial treatment when it is combined with pharmacotherapy for the treatment of alcohol-related problems. We must begin to use various biological and psychosocial indicators to identify which subtypes of alcoholic patients might benefit from certain pharmacotherapeutic agents. Further examination of alcoholic patients who have pharmacologically treatable psychiatric disorders will clarify the effect of specific 'stress reduction' on alcohol intake. The exploration of the ability of agonists and antagonists at specific 5-HT receptor subtypes to reduce alcohol consumption should be promising, especially in alcoholic patients who have psychiatric diagnoses that may involve 5-HT dysregulation (depression, bulimia, OCD, and antisocial personality disorders). Particular attention should be paid to the effect of these agents on the obsessional thinking and compulsive behaviours associated with drinking, a phenomenon shared across the range of impulsive and compulsive states.

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