

# Patient preferences and perspectives regarding reducing alcohol consumption: role of nalmefene

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**Abstract:** Alcohol use disorder is a major public health issue. The absolute mortality burden of alcohol-attributable death has increased over the last 20 years. However, access to care remains very poor and many people with alcohol use disorder are untreated. The main limiting factor for access to care in alcohol use disorder appears to be the reluctance to engage in abstinence. Risk reduction is a developing approach in the treatment of alcohol use disorders, drawing its inspiration, with quite a delay, from the decades-long dominant approach in other substance use disorders. A paradigm shift has recently occurred that places more of an emphasis on reducing alcohol as a therapeutic strategy for patients with alcohol use disorder, to better meet the patients' preferences and needs. The development and recent approval of nalmefene, in alcohol-dependent adults with a high drinking risk level, contributes to enlarging the therapeutic arsenal for alcohol dependence, strengthening the legitimacy of alcohol reduction strategies.

**Keywords:** harm reduction, alcohol use disorder, therapeutic goal, patients' satisfaction

## Introduction

Alcohol use disorder is a major public health issue. The absolute mortality burden of alcohol-attributable death has increased over the last 20 years.<sup>1,2</sup> Alcohol consumption is estimated to be responsible for 3.8% of all deaths.<sup>3</sup> The global costs of excessive drinking are estimated to exceed \$200 billion a year.<sup>3</sup> However, alcohol abuse and dependence present the widest treatment gap of all mental disorders, with 78.1% not treated for their alcohol use disorder in a given year.<sup>4,5</sup> The purpose of our article is to contextualize the recent emphasis on risk-reduction strategies in alcohol use disorders, in particular in the context of the approval of nalmefene, as part of an increase in client-centered approaches and a global shift in the representation of alcohol use disorders, supported by scientific advances.

## Alcohol drinking goals: alcohol reduction versus abstinence

Data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) large cohort reported that 75% of the subjects with a history of alcohol dependence the previous year were in partial or total remission from alcohol dependence. Only one third of them were ever treated.<sup>5</sup> These data support the fact that spontaneous remission from alcohol dependence can occur. However, in the NESARC cohort, only 18% of the subjects changed their consumption pattern to abstinence. Alternatively spontaneous reduction can also occur. However, a large portion of patients remain untreated and with difficulties. Reducing barriers to treatment is a tremendous challenge in alcohol use disorder. Stigma is part of the challenge. Stigma denigrates the value of people who have a mental illness, and the social and professional support

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systems designed to support them. Structural stigma, which refers to stigma from health professionals, has been documented in alcohol use disorder as a barrier to treatment.<sup>6</sup>

The main limiting factor for access to care in alcohol use disorder appears to be the reluctance to engage in abstinence.<sup>7</sup> In fact, the majority of patients seem to initially aim for a reduction in consumption.<sup>8,9</sup> A reduction in consumption is not proposed everywhere to the same extent to patients entering treatment,<sup>8</sup> and a perception of reduction in consumption is still evolving for alcohol specialist workers and varies across countries.

A paradigm shift has recently occurred that places more of an emphasis on reducing alcohol consumption among the range of therapeutic strategies for patients with alcohol use disorder. Namely, risk reduction has at least been considered in the alcohol use disorder field, whereas it has been the dominant approach in the fields of other substance use disorders since the 1980s. Acceptability of reduction of consumption among alcohol specialist workers still varies between countries, probably in part due to variations in local support provided by Alcoholics Anonymous.<sup>8</sup> Two major arguments in favor of alcohol reduction are to be highlighted. First, due to the exponential relationship between harmful events and alcohol consumption, any reduction in alcohol consumption, even a minimal one, could be considered to have a positive impact on the alcohol burden.<sup>3,10</sup> One of the other most striking arguments supporting integration of a reduction in consumption into the panel of therapeutic strategies in alcohol use disorder is that allowing the patient to choose the goal, either abstinence or non-abstinence, was found to be a better predictive factor of good outcomes than the goal itself.<sup>11</sup>

## Arguments for client-centered approaches in alcohol use disorder

This association between the choice of the therapeutic goal by the patient themselves and a good outcome is precisely the basis of the client-centered approach, as proposed in motivational interviewing,<sup>12</sup> upon which are based the majority of the psychotherapeutic interventions proposed in addiction treatment. Most of the psychotherapeutic interventions, aiming for a reduction in the consumption of alcohol, exclude subjects with severe alcohol use disorder.<sup>13</sup> Although a directive therapy, the motivational interviewing approach encourages the counselor to inquire about and respect the client's views and preferences during the treatment process. However, paternalist movements have most-likely interfered with this approach, leading to this contradiction.<sup>14</sup>

More recently, the neurosciences have revisited the long-standing clinical postulate that patients with alcohol

use disorder presented with denial, meaning that they could not choose their own goal. Denial is translated into cognitive difficulties, which prevent the patients from identifying some of the negative consequences of their alcohol use.<sup>15,16</sup> This finding is an important turn in the understanding of alcohol use disorder, because it reduces the stigma. Care is patient-focused, and treatment can be considered as recovering the skills to control alcohol use, not only to extract the patient from a drinking environment. Finally, this turn dissociates the symptoms from the choice of the therapeutic goal: reluctance to engage in abstinence could previously be perceived by health care providers as a kind of denial about the severity of the illness.

This association was supported by the former *Diagnostic and Statistical Manual of Mental Disorders* (DSM) IV classification, which implicitly proposed a hierarchical relation between abuse and dependence.<sup>17</sup> A common feature in clinical practice was to reserve reduction for abusers and to strongly advise abstinence for dependent subjects. This method is no longer suitable as the DSM 5 classification considers alcohol use disorder a continuum.<sup>18</sup> Moreover, one fear in proposing a reduction in consumption was that severe patients could be tempted to more-often choose non-abstinent goals due to denial about the severity of their illness, whereas they could be less successful in non-abstinent goals. The recent secondary analysis of the COMBINE study showed, on the contrary, that patients with the highest level of negative consequences linked to alcohol consumption more often choose abstinence.<sup>19</sup> However, returning to the premorbid state is a usual demand from patients suffering from any illness.<sup>20</sup> It should not be surprising that patients with alcohol use disorder also ask for this return to their premorbid state, namely, with a non-abstinent goal, which better fits with their habits and environment. As reported in the same secondary analysis of the COMBINE study, more daily drinkers in a social network predicted the choice of non-abstinent goals.<sup>19</sup> Nonadherence to life-style modification is a common feature of other chronic illnesses, for instance, among diabetic patients,<sup>21</sup> and it is then not considered denial but a therapeutic challenge. Efforts should focus on developing therapeutic options that could aid in developing recovery styles that are in harmony with the patient's environment, including their drinking environment, like taking stigmatization into account.<sup>22</sup>

The representations of alcohol use disorder are changing. Alcohol reduction, an acceptable therapeutic goal in dependent patients, accompanies these changes. Generalizing alcohol reduction in dependent patients requires a diversification of the psychotherapeutic arsenal and opening new

psychotherapeutic avenues, such as cognitive enhancement<sup>23</sup> or pharmacotherapy.

## The challenge of outcome measurement

From the perspective of developing new pharmacotherapies aiming at alcohol reduction, a focus on the relevant criteria to assess outcomes in these kinds of interventions is necessary. In fact, there is a need to enlarge the criteria used to assess outcomes in interventions aimed at reducing alcohol consumption; binary outcomes like abstinence (yes/no) are no longer relevant in this context. National and international authorities have recently provided guidelines for the development of drugs to reduce alcohol consumption in alcohol use disorder. In Europe, the criteria to assess the outcome, if aiming at alcohol reduction, should be either the number of heavy drinking days (HDD) or the total alcohol consumption.<sup>24</sup>

However, Sobell and Sobell have previously shown that the quantitative assessment of alcohol consumption is a complex issue. They showed that even when investigating a single set of patients in one trial, the modality of reporting alcohol consumption could make the success rate vary from 8% to 80%.<sup>25</sup> This analysis illustrates the limits of the quantitative criteria of alcohol consumption, the so-called “drinking outcomes”, to report the relevant clinical state in alcohol use disorder. The change in paradigm towards integrating the reduction of consumption in alcohol use disorder requires one to place a higher emphasis on qualitative assessments that are closer to patients’ concerns and more relevant clinically.

Recently, several qualitative concepts have emerged to measure patients’ clinical states and outcomes: negatively related consequences,<sup>26</sup> craving,<sup>27,28</sup> and health-related quality of life (HRQOL).<sup>29</sup> The concept of negative alcohol-related consequences has the disadvantage of coming from the expert’s point of view. In contrast, HRQOL reflects patients’ feelings and functioning, and the impact of their health condition beyond simple symptom assessment. HRQOL is recognized as an important outcome in alcohol-dependence research.<sup>30</sup> HRQOL, as well as craving and patient satisfaction, can adopt the patient’s point of view, and is often assessed with self-questionnaires. However, there is currently only one disease-specific HRQOL instrument for alcohol dependence that is developed from patients’ input: the Alcohol use disorder Quality of Life Scale.<sup>31</sup> Craving is believed to be the consequence of a complex neurobiological dysfunction, and it is now conceived as a therapeutic target itself.<sup>32</sup> Patient satisfaction has been poorly explored in the alcohol use disorder field.<sup>33</sup> Patient

satisfaction can be explored following multiple domains: 1) patient attendance; 2) therapeutic alliance; 3) patient satisfaction with medication; and 4) patient satisfaction with treatment setting.

## Patient attendance

Satisfaction is often equated to attendance or patient follow-up completion.<sup>34</sup> Studies in alcohol dependence often experience a high attrition rate, from half to two-thirds of the patients. However, attrition rates, as well as access to care, could be influenced by the kind of therapeutic goals proposed to patients. One patient reducing his consumption could feel discomfort at being included in an abstinence-oriented trial even if he could improve by simply reducing his alcohol intake. The attrition rate could be reduced in reduction-oriented trials and in trials that allow the patient to choose his own therapeutic goal.<sup>35,36</sup>

## Therapeutic alliance

Patient satisfaction can be approximated by therapeutic alliance, a concept that is similar to satisfaction with the medical management. It can be explored by scales such as the “Working alliance inventory” or the “patient satisfaction with medical management score”, as used in the COMBINE study.<sup>37</sup> In this study, patients were included if they were abstinent for at least 4 days. The working alliance improved significantly with the number of abstinent days and with the number of days without heavy drinking. Surprisingly, patient satisfaction with the medical management improved with the number of abstinent days but not with the number of days without heavy drinking.<sup>38</sup> This difference could show difficulties in managing patients who are aiming to reduce their consumption at this time.

## Patient satisfaction with medication

Patient satisfaction with the medication can be investigated. In the alcohol-dependence field, no direct measure of satisfaction with medication has ever been used to our knowledge. This kind of measure has, however, been developed in other mental disorders, such as bipolar disorder, with the PATient SATisfaction with Psychotropic (PASAP) scale, a self-completed questionnaire measuring satisfaction with psychotropic medication.<sup>39</sup> The development of this kind of measurement could be particularly useful in the context of emerging drugs in the alcohol field, with potentially high effect sizes but also potentially high secondary effects levels, to help document the benefit–risk balance of this medication.<sup>40</sup> This method could help in understanding dropout rates.

## Patient satisfaction with treatment setting

Patients' satisfaction with the treatment setting can be assessed. In the context of an unequally proposed reduction of consumption strategies and the deep reorganization of some clinics, that aim to give a higher place to this therapeutic goal, this change could be particularly interesting in assessing patients' satisfaction with in the health care setting for alcohol use disorder subjects. To our knowledge, this method has not been explored to date in alcohol use disorder, even though it has been used in the illicit-drug use disorder field. Once again, we could learn from the opiate use disorder risk-reduction model. The Randomised Injectable Opiate Treatment Trial (RIOTT) study investigates patients' pretreatment expectations of, and posttreatment satisfaction with, supervised injectable opiate treatment delivered within UK's first such clinics.<sup>41</sup> This kind of measure could be very useful to help change the representation of the illness to the general population and to support the development of new risk-reduction initiatives in the alcohol use disorder field as well.

## Nalmefene: a new treatment strategy

In the context of emphasis on risk-reduction strategies in alcohol use disorders, enhanced by increasing use of client-centered approaches, the recent European approval of nalmefene<sup>42</sup> is likely to be a historical step in the advancement of alcohol use disorder treatment. Nalmefene is the first drug to obtain approval for the reduction of alcohol consumption. Nalmefene received a marketing authorization valid throughout the European Union on February 25, 2013 and is under development in Asia. Nalmefene is an opioid system modulator with a distinct  $\mu$ ,  $\delta$ , and  $\kappa$  receptor profile. In vitro studies have demonstrated that Nalmefene is a selective opioid receptor ligand with antagonist activity at the  $\mu$  and  $\delta$  receptors and partial agonist activity at the  $\kappa$  receptor. In vivo studies have demonstrated that nalmefene reduces alcohol consumption, possibly by modulating cortico-mesolimbic functions.<sup>10</sup> Nalmefene showed a significantly superior effect as compared to placebo in the change in HDD from baseline to month 6 (group difference:  $-1.7$  days/month; 95% confidence interval [CI]  $-3.1$  to  $-0.4$ ;  $P=0.012$ ).<sup>43</sup> As demonstrated above, offering a large panel of therapeutic goals could greatly enhance the access to care, lowering barriers to treatment. Patients with alcohol use disorder should now be able to benefit from pharmacotherapy whatever their drinking goal.

Nalmefene is approved in alcohol-dependent adults with a high drinking-risk level.<sup>44</sup> This population is precisely the one that was previously prevented from reduction strategies

because these patients were considered to be too severely ill to be able to reduce their drinking. In contrast, in patients with at least a high drinking-risk level (men:  $>60$  g/day; women:  $>40$  g/day), nalmefene showed a superior effect as compared with placebo in reducing the number of HDD (treatment difference:  $-3.2$  days; 95% CI:  $-4.8$  to  $-1.6$ ;  $P<0.0001$ ) and total alcohol consumption (treatment difference:  $-14.3$  g/day; 95% CI:  $-20.8$  to  $-7.8$ ;  $P<0.0001$ ) at month 6.<sup>35</sup> In the long-term trial, a post hoc analysis of patients with at least a high drinking-risk level showed that nalmefene was more effective than placebo at month 13, both in the reduction of the number of HDD ( $-1.6$  days/month; 95% CI  $-2.9$  to  $-0.3$ ;  $P=0.017$ ) and the reduction of total alcohol consumption ( $-6.5$  g/day last month; 95% CI  $-12.5$  to  $-0.4$ ;  $P=0.036$ ).<sup>45</sup> The effect is unclear for patients with a lower risk level, who are most likely to receive much benefit from psychosocial management that targets reduction, regardless of the medication. Most severe patients are then indeed able to reduce their consumption. These results of quantitative drinking endpoints should be completed with alternative endpoints closer to patients' concerns, such as craving, and especially HRQOL and patients' satisfaction.

The regimen of nalmefene also involves the patients' preference: nalmefene was approved for "as-needed" use.<sup>42</sup> Patients were told to take their medication only if they felt the need to take it, if they anticipated an at-risk situation, or as soon as possible if they already had started to drink alcohol. This is a patient-centered approach that engages patients with alcohol dependence in the active management of their illness. The feasibility of this regimen has been established. Sixty-eight percent of nalmefene-treated patients (78% of the study completers) adhered to the as-needed treatment regimen on at least 80% of the study days.<sup>46</sup>

As-needed oral nalmefene was generally well tolerated in patients with alcohol dependence, according to the results of the three European randomized, double-blind, multinational trials: ESENSE 1, ESENSE 2, and SENSE.<sup>44</sup> The treatment-emergent adverse events that led most-commonly to discontinuation (occurring in  $\geq 2\%$  of nalmefene recipients) included dizziness, nausea, fatigue, and headache.<sup>44</sup>

## Conclusion

The development and recent approval of nalmefene contributes to enlarging the therapeutic arsenal for alcohol dependence, strengthening the legitimacy of alcohol-reduction strategies. With an as-needed regimen, nalmefene increases patients' feelings of responsibility within the treatment process. This



new pharmacotherapy contributes to a larger movement and interest in reduction strategies that began several decades ago. In one sense, there is only one goal of treatment for alcohol use disorders: to improve the user's quality of life. This goal may seem obvious but can easily be forgotten when there is an exclusive preoccupation with drinking behavior.<sup>47</sup> One should keep in mind that either abstinence or alcohol reduction are merely means to attain the therapeutic goal.

## Disclosures

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