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Amandine Luquiens

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Amandine Luquiens. Qualité de vie dans le trouble d'usage d'alcool : une mesure de l'effet thérapeutique du point de vue des patients. Médecine humaine et pathologie. Université Sorbonne Paris Cité, 2015. Français. NNT : 2015USPCB118 . tel-01541568

HAL Id: tel-01541568

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Thèse de science, spécialité sciences cognitives, Université Paris Descartes

Qualité de vie dans le trouble d'usage d'alcool: une mesure de l'effet thérapeutique du point de vue des patients.

Ecole doctorale ED3C

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Aux patients d'addictologie de l'hôpital Paul Brousse, qui m'ont expliqué leur souffrance et m'ont appris à sans cesse la remettre au centre de mes préoccupations, tant en clinique qu'en recherche.

A tous les patients qui ont participé aux études présentées dans cette thèse, et qui ont donné leur temps et partagé leur précieuse expérience, souvent chargée d'émotions, pour m'aider à mieux les comprendre.

Remerciements

Je remercie Henri-Jean Aubin qui m'a fait découvrir à la fois l'addictologie et la recherche, et continue chaque jour à me transmettre avec patience et bienveillance un peu de ses connaissances. Tu m'as fait confiance et a su comme toujours « catalyser » mon travail. J'apprends bien plus que mon métier en travaillant avec toi.

Je remercie Bruno Falissard pour ses conseils à toute heure et depuis tous les points de la terre ! Merci de ton soutien sans faille et de participer à ce jury.

Je remercie les Laboratoires Lundbeck qui ont financé le développement de l'échelle AQoLs et accepté de l'intégrer dans de nombreux protocoles. Merci pour votre confiance et d'avoir cru en ce projet. Je remercie en particulier Philippe Laramée qui a rendu cette aventure possible !

Je remercie RTI et Creativ Ceutical pour leur aide et leur grande expérience.

Je remercie Michel Reynaud et Amine Benyamina qui m'ont initiée à l'addictologie et m'ont fait confiance.

Je remercie George Brousse qui me fait la grande gentillesse de rapporter et juger ce travail ainsi que pour son accueil chaleureux à Clermont Ferrand.

Je remercie Maurice Demateis qui me fait également l'honneur et la gentillesse de rapporter et de juger ce travail. J'apprends mille choses à chacune de nos rencontres et l'addictologie devient limpide tout à coup !

Je remercie Marie Grall-Bronnec qui me fait l'honneur et la gentillesse de se déplacer de Nantes et de participer à ce jury. Ton expérience auprès des joueurs, tu le sais, m'as appris énormément ; nos échanges au sein du réseau sont une bouffée d'oxygène ! Je suis heureuse de bénéficier maintenant de ton expérience en alcoologie.

Je remercie Caroline Dubertret qui m'a vue jeune externe puis interne, et dont j'apprécie toujours la bienveillante sollicitude ; tu avais déjà accepté de te pencher sur ce travail lors du comité de thèse et je te remercie d'avoir accepté de continuer à suivre ce travail et à le juger.

Je remercie Franck Bellivier qui me fait l'honneur de participer à ce jury et après avoir déjà participé à mon comité de thèse et avait guidé mes réflexions avec une grande rigueur.

Je remercie ma famille et en particulier mes enfants Louise et Sacha ainsi que mon mari Guillaume pour leur patience et leur soutien lors des séances de rédaction estivale, et tout le reste du temps !

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Liste des publications présentées dans cette thèse [Journal Impact Factor]

1. Luquiens, A., Reynaud, M., & Aubin, H. J. (2011). Is controlled drinking an acceptable goal in the treatment of alcohol dependence? A survey of French alcohol specialists. *Alcohol Alcohol* 46, 586-91. [Journal Impact Factor 2.09]
2. Luquiens, A., & Aubin, H. J. (2014). Patient preferences and perspectives regarding reducing alcohol consumption: role of nalmefene. *Patient Prefer Adherence* 8, 1347-52. [Journal Impact Factor 1.49]
3. Luquiens, A., Reynaud, M., Falissard, B., & Aubin, H. J. (2012). Quality of life among alcohol-dependent patients: How satisfactory are the available instruments? A systematic review. *Drug Alcohol Depend* 125, 192-202. [Journal Impact Factor 3.28]
4. Francois, C., Rahhali, N., Chalem, Y., Sorensen, P., Luquiens, A., & Aubin, H. J. (2015). The Effects of as-Needed Nalmefene on Patient-Reported Outcomes and Quality of Life in Relation to a Reduction in Alcohol Consumption in Alcohol-Dependent Patients. *PLoS One* 10, e0129289. [Journal Impact Factor 3.23]
5. Luquiens, A., Whalley, D., Crawford, S. R., Laramée, P., Doward, L., Price, M., Hawken, N., Dorey, J., Owens, L., Llorca, P. M., Falissard, B., & Aubin, H. J. (2014). Development of the Alcohol Quality of Life Scale (AQoLS): a new patient-reported outcome measure to assess health-related quality of life in alcohol use disorder. *Qual Life Res* 24, 1471-81. [Journal Impact Factor 2.86]
6. Luquiens, A., Owens, L., Rahhali, N., Whalley, D., Crawford, S., Laramée, P., Doward, L., Price, M., Hawken, N., Dorey, J., Llorca, P., Falissard, B., & Aubin, H. ([DRAFT]). Quality of life in alcohol dependence: similar cross-cultural impact beyond specific drinking habits.
7. Luquiens, A., Whalley, D., Laramée, P., Falissard, B., Kostogianni, N., Rehm, J., Manthey, M., Paille, F., & Aubin, H. J. (in Rev). Validation of a new patient reported outcome instrument of health-related quality of life specific to patients with alcohol use disorder: the Alcohol Quality Of Life Scale (AQoLS). *Quality of life research* [Journal Impact Factor 2.86]
8. Whalley, D., Crawford, S., Laramée, P., Higuchi, S., Hao, W., Kim, S., Luquiens, A., & Aubin, H. ([DRAFT]). Cultural Adaptation of the Alcohol Quality of Life Scale for Use in Japan, China, and South Korea.

(Liste des autres publications du candidat sans rapport avec la thèse en annexe 8)

Résumé

Contexte :

L'évolution des pratiques en alcoologie, suivant le modèle des soins centrés sur la patient, permet de revisiter le concept de rémission pour une meilleure prise en compte du point de vue du patient, participant de façon prépondérante dans la définition de ses objectifs thérapeutiques et dans leur évaluation. Pourtant, peu de ces critères subjectifs de l'évaluation du devenir des patients ont véritablement inclus le patient dans leur développement. Jusqu'à récemment, les instruments mesurant la qualité de vie les plus utilisés en alcoologie étaient génériques, constitués d'items générés par les experts et s'appuyant sur la littérature existante, mais n'ayant pas impliqué de patient dans leur développement, c'est-à-dire dans la génération des items.

Méthodes : nous avons réalisé une revue systématique de la littérature recensant les essais thérapeutiques randomisés testant une intervention chez les patients alcoolodépendants, et mesurant son efficacité sur la qualité de vie. Nous avons répertorié les dimensions explorées dans les instruments existants. Il a été montré que ces instruments n'exploraient pas de façon optimale l'impact de l'alcoolodépendance sur la qualité de vie. Sur ce constat, nous avons développé conformément aux recommandations de la Food and Drug Administration (FDA) sur le développement des « Patients-Reported Outcomes » une échelle spécifique au trouble d'usage d'alcool, à partir du vécu rapporté par les patients. Nous avons utilisé la méthode des groupes focus, réalisés en parallèle en France et en Grande-Bretagne auprès de 38 patients présentant un trouble d'usage d'alcool. Ces groupes ont pu générer un pool d'items, testés secondairement par des entretiens cognitifs individuels auprès de 31 patients, aboutissant à l'échelle finale « Alcohol Quality of life Scale » (AQoLS). Nous avons ensuite validé l'échelle AQoLS sur un échantillon de 285 patients français présentant un trouble d'usage d'alcool, recrutés dans des centres sélectionnés de façon aléatoire en France.

Résultats : L'échelle développée comporte 34 items, répartis selon 7 dimensions : les relations sociales, les activités, les conditions de vie, s'occuper de soi, les émotions négatives, le sommeil et la perte de contrôle. L'analyse de l'échelle a pu confirmer 6 de ces sept dimensions, avec une répartition légèrement différente des items. La dimension « s'occuper de soi » a disparu au profit d'une nouvelle dimension, l'estime de soi. Les dimensions de contrôle et d'estime de soi sont novatrices dans un instrument de qualité de vie liée à la santé, chez l'adulte. L'échelle a montré de bonnes propriétés psychométriques, avec une bonne consistance interne (Cronbach = 0.96), et une corrélation modérée mais significative avec certains sous-scores de la SF-36 et l'EQ-5D. Un travail complémentaire qualitatif a pu illustrer les liens entre les différents domaines impactés, et notamment la proximité de perception dans les propos des patients, entre l'estime de soi, la perte de contrôle et les troubles cognitifs.

Conclusion

L'évolution vers un modèle des soins centrés sur le patient permet d'envisager une conception différente de la rémission et de construire et valider une mesure de la qualité de vie se rapprochant des préoccupations des patients, l'échelle AQLS. Deux dimensions novatrices ont été rattachées à ce concept : la perte de contrôle du point de vue du patient, et l'estime de soi.

Liste des abbréviations

APQ : Alcohol Problems Questionnaire

AQoLS: Alcohol Quality of Life Scale

CDT : Carbohydrate Deficient Transferrin

EMA : European Medicine Agency

EQ5D: EuroQol 5 Dimensions

FDA: Food and Drug Administration

GGT Gamma-Glutamyl Transferase

NICE: National Institute for Health and Clinical Excellence

OCDS: Obsessive Compulsive Drinking Scale

PRO: Patient Reported Outcome

Q-LES-Q : Quality of Life Enjoyment and Satisfaction Questionnaire

QV : Qualité de Vie

QVLS : Qualité de Vie Liée à la Santé

SFA: Société française d'alcoologie

SF-36: Medical Outcomes Study 36-Item Short-Form Health Survey

TOMHS-HWBS: Treatment of Mild Hypertension Study Health and Well-being Scale

TUA : Trouble d'Usage d'Alcool

UCE : Unités de Contexte Élémentaires

VAS : Visual Analog Scale

WHO-QOL-26: World Health Organization Quality of Life Assessment Instrument

Introduction

Méthodes d'évaluation de l'effet thérapeutique en alcoologie

Les méthodes d'évaluation de l'effet thérapeutique en alcoologie ont beaucoup évolué ces dernières années. L'intégration des objectifs de réduction de consommation à côté de celui de l'abstinence a mis en évidence le caractère limité de la simple évaluation d'une quantité d'alcool consommée dans les essais thérapeutiques. De plus, l'évolution des pratiques suivant le modèle des soins centrés sur le patient - qui concerne l'ensemble de la médecine - permet de revisiter le concept de rémission pour une meilleure prise en compte du point de vue du patient, participant de façon prépondérante dans la définition de ses objectifs thérapeutiques. En effet, la modification des consommations ne semble pas être un objectif pour le patient mais plutôt un moyen de faire évoluer son état. De plus, l'amélioration des symptômes tels que décrits par le soignant ne correspond pas toujours à l'objectif du patient, tout du moins à ce qui l'amène à demander le soin.

Dans les essais: la quantité d'alcool consommée comme critère principal

Les mesures relatives à la consommation d'alcool sont considérées comme le critère principal à privilégier par les autorités de santé (EMA 2010; FDA 2015). Elles tentent de refléter la fréquence, l'intensité et la durée des consommations d'alcool après l'initiation du traitement. Les quantités d'alcool ou le statut par rapport à l'abstinence sont souvent auto-rapportées, pour des raisons aussi bien pratiques (patients ambulatoires), que d'alliance thérapeutique. On ne peut cependant pas à proprement parler de mesure subjective, et ces mesures sont souvent considérées comme des critères "durs". Le National Institute for Health and Clinical Excellence (NICE) distingue deux types de mesures concernant les consommations d'alcool: les critères dichotomiques et les critères continus. Ces derniers incluent: (1) l'abstinence mesurée en pourcentage / proportion de jour d'abstinence, (2) la période la plus longue d'abstinence (3) la quantité d'alcool consommée, par exemple en verres par jour, moyenne de nombre de verre par semaine, nombre de verre par épisode,

quantité totale d'alcool consommé par jour. En effet, il paraît difficile, et en particulier dans les essais visant la réduction de consommation, de se contenter de variables binaires de type abstinence oui/non, et l'agence européenne médicament recommande pour ces derniers l'utilisation de critères quantitatifs, de type quantité totale d'alcool consommée par jour ou pourcentage de jours de consommation excessive (EMA 2010). Cependant, après avoir proposé en 2005 un critère continu, le pourcentage de jour de consommation excessive (Allen and Wilson 2003), la récente mise à jour des recommandations américaines par la Food and Drug Administration (FDA) portant sur le développement des produits de santé en alcoologie stipule que le critère demandé pour les essais ne visant pas l'abstinence devrait plutôt être un critère catégoriel, à savoir aucun jour de consommation excessive. La rigueur de ce critère impose la précaution d'une période de grâce d'environ 15 jours, et le caractère perfectible de ces recommandations a été souligné par le groupe ACTIVE (Anton, Litten et al. 2012; FDA 2015). Parmi les essais les plus récents, 68% des essais rapportent des mesures de types continus des consommations d'alcool (Robinson, Sobell et al. 2014). En effet, les modalités de report de la consommation d'alcool reposant sur des seuils (variables catégorielles de type consommation au-dessus vs au-dessous du seuil), par jour, semaine ou mois peuvent faire varier le taux de succès d'un essai de 8% à 80% pour les mêmes patients (Sobell, Sobell et al. 2003). La mesure de la quantité d'alcool consommée ne peut pas être mesurée totalement objectivement, et est du ressort de l'impression du patient, et donc soumise à sa propre conception d'un verre, de l'abstinence, de l'alcool en général. Cette conception peut varier sensiblement, malgré les consignes données pour le recueil et une sensibilisation à la standardisation de celui-ci. Ce recueil est facilité par certains instruments, comme le Time Line Follow Back, développé par Sobell et recommandé par l'American Psychiatric Association (Sobell, Brown et al. 1996; APA 2000). Cet instrument a la forme d'un calendrier de consommation, s'appuyant sur des événements ayant marqué la période interrogée pour favoriser la fidélité du recueil rétrospectif. Sa période de rappel varie de quelques jours à plusieurs années. Il peut être auto-administré ou administré par un clinicien entraîné. Ces techniques pourraient évoluer avec l'intégration de

technologies de type smartphone permettant un recueil prospectif et en temps réel des consommations (Serre, Fatseas et al. 2015).

La FDA propose que ces estimations soient autant que possible complétées par des mesures biologiques (FDA 2015). Elles peuvent concerner des mesures indirectes de l'intoxication alcoolique, telles que le volume globulaire moyen, les gamma-glutamyl transferase (GGT), la Carbohydate deficient transferrin (CDT), les transaminases. Cependant, ces mesures prennent souvent des semaines voire des mois à se normaliser après le début de l'abstinence, et reflètent mal les rechutes transitoires. Plus précisément, la CDT augmente et se normalise plus rapidement que les GGT: en réaction d'une alcoolisation excessive, la CDT augmente dans la semaine, et se normalise dans les 1 à 3 semaines, alors que les GGT ne donnent qu'une vision globale sur 1 à 2 mois (Drummond, Ghodse et al. 2007). Ces marqueurs ne reflètent donc qu'une tendance globale de la consommation d'alcool. De plus, à l'exception de la CDT, la spécificité et la sensibilité de ces marqueurs sont faibles (Sillanaukee 1996). Cependant, ces marqueurs font partie de l'évaluation recommandée par le NICE, en particulier de façon combinée (CDT et GGT), et associée avec d'autres types de critères (Drummond 2010). Ces marqueurs ont été utilisés comme critère principal de jugement dans certaines études anciennes et sont désormais plutôt utilisés comme critère secondaire, dont l'utilisation peut être justifiée pour confirmer un résultat reposant sur des seules mesures subjectives.

La quantité d'alcool consommée semble importante à documenter, notamment car elle a été associée à la mortalité et la morbidité (Rehm and Roerecke 2013). Rehm a été jusqu'à la proposer pour remplacer les critères diagnostiques complexes de l'addiction (Rehm, Marmet et al. 2013). Cependant cette proposition fait toujours l'objet d'une grande controverse, lui reprochant de passer à côté de ce qui caractérise l'addiction (Heather 2013). Pourtant, le concept de pertinence clinique ("clinical relevance") est requis par la FDA, qui considère que les essais doivent être construits à priori pour la démontrer (ICH 1998). Il était déjà noté dans ce rapport ancien que les catégorisations aboutissaient à une perte d'information, et que les

critères d'évaluation devaient être choisis pour servir la notion de pertinence clinique. Pourtant ce concept se pose dans une certaine contradiction avec les éléments présentés ci-dessus, tant par la demande des autorités de santé américaines de rapporter des mesures catégorielles que par le recentrage des mesures autour de la quantité d'alcool consommée, dont la pertinence on l'a vu peut paraître limitée. De plus, certains auteurs ont relié le concept de pertinence clinique à celui de signification dans la vie "meaning in life", c'est à dire la capacité d'un critère à prédire le bien être ultérieur d'un sujet (Debats 1996). Ce concept peut paraître assez vide si on le limite à une quantité d'alcool consommée.

La mesure seule de l'alcool consommé présente des limites en terme de représentation du devenir réel du patient, et ont abouti à la volonté de décrire de façon plus fine celui-ci, dans les domaines sur lesquels retentissent ces consommations, proches des préoccupations du patient et qui sont finalement ceux qui motivent le patient à venir consulter et surtout à changer celles-ci (Anton, Litten et al. 2012). 56 % des essais seulement rapportent des mesures complémentaires non relatives à l'alcool consommé (Robinson, Sobell et al. 2014).

Du point de vue du clinicien (Luquiens et al. 2011)

La généralisation des résultats des essais à la population générale paraît difficile, d'abord par l'inclusion de patients trop "purs", c'est à dire sans comorbidité ou trop précaires. (Blanco, Olfson et al. 2008). Cela pourrait contribuer au fait que les cliniciens se saisissent peu des résultats des essais cliniques pour choisir leur stratégie thérapeutique. Cependant, ce manque de généralisabilité pourrait ne pas être le seul facteur expliquant le peu de retentissement de la littérature scientifique sur la pratique clinique. Dans une enquête en ligne anonyme réalisée en 2009, nous avons interrogé systématiquement les alcoologues adhérant à la Société française d'alcoologie, sur les critères de succès qu'ils utilisaient pour leurs patients en pratique clinique, et ceux qu'ils pensaient devoir être utilisés dans les essais cliniques. 216 alcoologues, soit près de 50% des adhérents, avaient répondu à cette

enquête, dont le sujet principal était l'acceptabilité de la consommation contrôlée d'alcool comme objectif thérapeutique dans l'alcoolodépendance. Nous avons retrouvé que la qualité de vie était le critère le plus utilisé en clinique par les alcoologues pour évaluer le succès chez leurs patients (critère principal pour 60% des alcoologues, tableau 2 ci-dessous) (Luquiens, Reynaud et al. 2011). Pourtant, peu d'entre eux attendaient que celle-ci soit documentée dans les essais cliniques (12%). L'absence de consensus sur la méthode de mesure de la qualité de vie et l'absence de mesure spécifique de la qualité de vie dans le trouble d'usage d'alcool avaient été émises comme hypothèses expliquant ce décalage.

Tableau 2 traduit de Luquiens, A., M. Reynaud, et al. (2011). "Is controlled drinking an acceptable goal in the treatment of alcohol dependence? A survey of French alcohol specialists." *Alcohol Alcohol* 46(5): 586-91 :

Critère principal de succès dans le traitement de l'alcoolodépendance	n (%)
Critère privilégié de succès utilisé dans la pratique clinique (n = 216)	
Conséquences négatives liées à l'alcool	17 (7.8)
Critères de dépendance	15 (6.9)
Critères d'abus	1 (0.5)
Nombre de jours de consommation excessive	0 (0)
Nombre de verres par jour	1 (0.5)
Nombre de jours d'abstinence et nombre de verres par jour	13 (6.0)
Nombre de jours d'abstinence	35 (16.1)
Absence de faux pas	5 (2.3)
Qualité de vie	130 (59.9)
Critère de jugement principal attend dans les essais cliniques (n = 173)	
Conséquences négatives liées à l'alcool	31 (17.9)
Critères de dépendance	8 (4.6)
Critères d'abus	4 (2.3)
Nombre de jours de consommation excessive	25 (14.5)
Nombre de verres par jour	1 (0.6)
Nombre de jours d'abstinence et nombre de verres par jour	3 (1.7)
Nombre de jours d'abstinence	4 (2.3)
Absence de faux pas	77 (44.5)
Qualité de vie	20 (11.6)

ORIGINAL ARTICLE

Is Controlled Drinking an Acceptable Goal in the Treatment of Alcohol Dependence? A Survey of French Alcohol Specialists

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(Received 23 March 2011; in revised form 21 June 2011; accepted 21 June 2011)

Abstract — **Aim:** Assessing acceptance of controlled drinking (CD) among French alcohol specialists. **Methods:** On-line survey of 547 French alcohol specialists. We searched factors associated with acceptance of CD, and factors that affected the specialists' selection of treatment goal. Criteria for success used by specialists in clinical practice were compared with criteria expected to be used in clinical trials. **Results:** CD was accepted as a treatment goal by 48.6% of alcohol specialists ($n=105$, $n=216$), and 61.9% practiced CD for their own patients ($n=130$, $n=210$). Factors in selecting outcome goals were: patient's choice, perceived self-efficacy, relapse history and severity of dependence. Age, profession and basis of specialists' opinion on CD were associated with acceptance of CD. **Conclusion:** Half of French alcohol specialists accept CD as a goal. Acceptance was associated with specialists' personal and professional characteristics. The criteria for success specialists use in their clinical practice differ from those they expect to be used in clinical trials.

INTRODUCTION

Controlled drinking (CD) has been a controversial subject since the early 1960s in the USA (Ambrogne, 2002), and subsequently in the rest of the world, and at that time divided the field of alcohol treatment into two entities with different therapeutic goals, abstinence or non-abstinence.

There is still no agreed definition of CD as an outcome. Control can be understood as either a quantitative or qualitative meaning. One could control how much one drinks, or alternatively control drinking consequences, and some authors have proposed integrating these two dimensions in the definition of CD as an outcome (Rosenberg, 2002). Quality of life is increasingly being assessed in studies of alcohol dependence (Foster *et al.*, 2000) in line with the current World Health Organization definition of health in a way that is closer to well-being, rather than a simple absence of disease.

In addition, there is currently no consensus on outcomes that should be used in the treatment of alcohol dependence, which further complicates comparison of abstinence versus non-abstinence goals (Heather and Tebbutt, 1992). In 2001, the National Institute on Alcohol Abuse and Alcoholism determined a sentinel criterion to be the percentage of heavy drinking days (Allen, 2003), whereas the European Medicines Agency recently defined two possible primary endpoints in the assessment of the efficacy of drugs for alcohol dependence: 'a full abstinence goal', considered to be 'relapse prevention after detoxification', and 'an intermediate harm reduction goal', considered to be a moderation of the quantity of alcohol consumed. CD should not be a final goal (EMA, 2010).

Several early studies that reported resumed normal drinking outcomes from abstinence-oriented treatment led to controversy. The first study, by Davies, reported on seven English alcohol-dependent patients who returned to CD, out of a group of 93 subjects (Davies, 2011). A second study (the Rand report) presented longitudinal 18 months data

from a cohort of 600 men treated for alcohol dependence: at 18 months, 22% were drinking moderately, whereas 24% were abstinent (38% were lost to follow up) (Polich *et al.*, 1980). In this study, the criteria for remission were either abstinence or 'normal drinking', defined as '(a) daily consumption less than three oz of ethanol, (b) typical quantities on drinking days less than five oz, (c) no tremor reported and (d) no evidence of frequent episodes of ≥ 3 of the following: (i) blackout, (ii) missing words, (iii) morning drinking, (iv) missing meals and (v) being drunk'. A study by Sobell and Sobell (1973) probably provoked most debate. It was a randomized clinical trial of 70 subjects, who followed either an abstinence-oriented or a CD-oriented therapeutic programme; the latter focused on loss of control. Opponents of a CD goal objected to various methodological problems in these studies, such as small sample sizes, short follow-up periods or biased samples (e.g. male-only cohorts). At the time, this controversy had little impact on clinical practice, at least in the USA (Peele, 1987). This impact has nevertheless been more important in other countries (Robertson and Heather, 1982).

More recent comparisons of abstinence and CD goals have given conflicting results. The main argument for the goal of CD is that imposition of abstinence as the sole treatment aim could pose an obstacle to treatment access (Sobell and Sobell, 1995). Furthermore, some people spontaneously resolve their alcohol dependence with CD outcomes (Dawson *et al.*, 2005). Some authors have attempted to identify criteria that may select people who could benefit from a mode of treatment aimed at CD: young age, marital status, dependence severity and confidence in the therapeutic goal may be associated with a positive outcome (Heather and Robertson, 1983; Hodgins, 2005). Self-selection of the therapeutic goal by the patient himself has been described as having a positive impact on the outcome. However, other authors take the view that abstinence should be the only goal, highlighting neurobiological arguments such as neural sensitization (Owen and Marlatt, 2001). Cultural and societal

factors that influence assessment and perception of therapeutic goals in the treatment of alcohol dependence have also been described (Peele, 1987).

Acceptance of CD as a goal, and its use in clinical practice, varies internationally. The acceptability of CD as a goal has been investigated in several countries since the early 1990s. In Australia, Britain, Norway and—more recently—Switzerland, CD as a goal is widely accepted by those treating alcohol dependence (Rosenberg *et al.*, 1992; Donovan and Heather, 1997; Klingemann and Rosenberg, 2009), whereas most treatment services in the USA do not accept CD as a goal (Rosenberg and Davis, 1994). Acceptability of CD as a goal appears to be mixed in Canada; one survey reported that 40% of treatment services questioned accepted CD as a goal (Rosenberg *et al.*, 1996). As far as we are aware, no data on the acceptability of CD as a goal in France have been published. France has a special relationship with alcohol through its history and societal habits; alcohol production and marketing is one of the most emblematic and traditional mainstays of the French economy (INSERM, 2003). It is therefore of particular interest to assess acceptance of CD as a goal, and determine its use in clinical practice, in France.

Our study had four main objectives: to assess the acceptance of CD as a goal among French specialists in the treatment of alcohol dependence; to investigate patient characteristics that influence the specialists' selection of non-abstinence as a therapeutic goal; to identify independent factors associated with specialists' acceptance of CD as a goal; to assess outcome criteria used by specialists in clinical practice, compared with the criteria they expect to be used in clinical trials.

MATERIALS AND METHODS

Study design and participants

This was an on-line survey performed among members of the French Society of Alcoholology [Société Française d'Alcoologie (SFA)]. The 547 members of the society who had registered an e-mail address when they joined were sent an e-mail inviting them to complete a questionnaire anonymously. Each specialist in the treatment of alcohol could complete the questionnaire only once. Our findings cannot be generalized to all French alcohol specialists, since we chose to include only SFA members for practical reasons. Moreover, some SFA members did not provide an e-mail address, so these could not be included in our study. However, those individuals represented a minority of SFA members, thus selection bias should have been limited. The survey was approved by an Ethics Committee (Comité National Informatique et Libertés).

Data collected

The following data were collected: (a) socio-demographic characteristics of specialists; (b) the specialist's school of theory, which influenced treatment type; (c) length of experience in the field of alcohol treatment; (d) whether working in an institution, type of institution (residential, out-patient or mixed), and acceptability of CD as a goal by the institution; (e) information on the type of patients treated, including age

and substances involved; (f) specialists acceptance of CD as a goal, and its use in clinical practice, including the percentage of his/her patients who initially aim for CD, and the percentage of patients for whom the specialist considers aiming CD to be appropriate; (g) definition of CD as an outcome, including threshold number of drinks, return to drinking without any abuse or dependence criterion, return to satisfactory quality of life, or drinking without negative consequence; (h) specialists' basis for opinion of goal of CD: scientific research, professional experience, personal experience, school of theory, institution's policy on CD as a goal; (i) specialist's preferred criterion for successful treatment of alcohol dependence in clinical practice; (j) expected primary endpoint in clinical trials of alcohol dependence.

Statistical analyses

Analyses were performed using R software, version 3.8. Descriptive analyses were performed for the total sample (all respondents) and in two subgroups (respondents who either accepted or rejected CD as a therapeutic goal). Univariate analyses were performed to compare these two groups, using *t*-tests for comparisons of means and either chi-square or Fisher tests to compare percentages. A logistic regression was performed to investigate specialists' acceptance of CD as a goal; all variables that were statistically significantly different between the two groups in the univariate analysis were included in the multivariate model, with the exception of success criteria in clinical practice (this factor had a large coefficient standard deviation, due to a sample size that was too small in some categories and probable colinearity with other variables, which disturbed the model). Definition of CD as an outcome was included in the model even if univariate comparisons were not statistically significant, in order to respect our initial hypothesis that opposed qualitative and quantitative definitions. The final variables included in the model were: specialists' age, profession, school of theory, whether working in an institution, basis of opinion on goal of CD, and definition of CD as an outcome. All tests were two-sided and at a significance level of 5%.

RESULTS

Responses were received from 263 (48.1%) of the 547 specialists to whom the questionnaire was sent. Two-thirds of the respondents (65.8%, $n = 173$, $n = 263$) answered all the questions in the survey. The pivotal question, regarding acceptance of CD, was answered by 82.1% of respondents ($n = 216$, $n = 263$).

Characteristics of all respondents are described in Table 1.

Demographic characteristics of responders were very similar to those of the entire membership of the SFA. Our sample consists of 74.5% of physicians, 72.5% of physicians within the SFA. It consists of 10.2% of psychologists, 10% in the SFA. Geographical distribution in our sample is also very close to that of the SFA: 27–26% in Ile-de-France, 17–19% in the Northeast, 16.3–17% in the Southeast, 5–11% in the Southwest, 26.2–19% in the Northwest, 1.3–2% in the Dom-Tom, 6–6.48% abroad.

CD was considered to be an acceptable treatment goal by 48.6% of respondents ($n = 105$, $n = 216$), although 61.9%

Table 1. Description of all specialists and by group accepting or rejecting controlled drinking. Comparisons between the two groups

Characteristics	All	Accept CD n (%)	Reject CD n (%)	P-value from χ^2 , Fisher exact test or t-test	P-value from logistic regression ^a
Age (n = 239) (mean \pm SD)	51.7 \pm 10.0	48.8 \pm 9.6	54.0 \pm 9.2	<0.001	0.002
Professional experience					
Professional background (n = 216)				<0.001	0.134
Hepato-gastroenterologist	14 (5.7)	3 (21.4)	11 (78.6)		
Other medical speciality	19 (8.7)	9 (47.4)	10 (52.6)		
General practitioner	85 (42.5)	47 (55.3)	38 (44.7)		
Psychiatrist	38 (17.6)	26 (68.4)	12 (31.6)		
Psychologist	22 (10.2)	11 (50.0)	11 (50.0)		
Other	38 (17.6)	9 (23.7)	29 (76.3)		
Length of professional experience (n = 216)				0.551	
No professional experience	5 (2.3)	3 (0.6)	2 (0.4)		
Less than 15 years	79 (36.6)	42 (53.2)	37 (46.8)		
More than 15 years	132 (61.1)	60 (45.51)	72 (54.5)		
School of theory (n = 216)				0.023	0.297
Motivational interviews	75 (34.7)	35 (46.7)	40 (53.3)		
Cognitive-behavioural therapy	43 (19.9)	28 (65.1)	15 (34.9)		
Psychodynamic	37 (17.1)	20 (54.1)	17 (45.9)		
Pharmacologic	16 (6.8)	6 (37.5)	10 (62.5)		
Twelve Steps	14 (6.5)	1 (7.1)	13 (92.9)		
Systemic	9 (4.2)	4 (44.4)	5 (55.6)		
Other	22 (10.2)	11 (0.5)	11 (0.5)		
Clinical setting					
Type of product (except tobacco) (n = 216)				0.110	
Alcohol only	47 (21.8)	18 (38.3)	29 (61.7)		
Alcohol and/or other products	169 (78.2)	87 (51.5)	82 (48.5)		
Institution	180 (83.3)	96 (53.3)	84 (46.7)	0.002	
Patients' status (n = 180)				<0.001	
Inpatient only	25 (13.9)	8 (29.6)	17 (63.0)		
Inpatient and outpatient	103 (47.7)	49 (47.6)	54 (52.4)		
Outpatient only	52 (28.9)	39 (0.75)	13 (0.25)		
Institution's acceptance of CD (n = 180)	86 (47.8)	78 (90.7)	8 (9.3)	<0.001	
Attitude and opinion					
Definition of CD (n = 176)				0.056	0.191
Drinking below a threshold	30 (17.0)	11 (36.7)	19 (63.3)		
Drinking without negative	40 (22.7)	17 (42.5)	23 (57.5)		
Return to drinking without	36 (20.5)	19 (52.8)	17 (47.2)		
Return to satisfactory quality of life	70 (39.8)	44 (62.9)	26 (37.1)		
Practices CD (n = 210)	130 (61.9)	91 (70.0)	39 (30.0)	<0.001	
Foundation of opinion on CD (n = 181)					
Scientific research	2.9 \pm 1.4 ^b	32 (47.8) ^c	35 (52.2) ^c	0.036	0.510
Professional experience	4.0 \pm 1.3 ^b	78 (56.1) ^c	61 (43.9) ^c	<0.001	0.039
Personal experience	2.6 \pm 1.6 ^b	21 (35.0) ^c	39 (78.0) ^c	0.005	0.003
School of theory	3.1 \pm 1.3 ^b	40 (54.8) ^c	33 (45.2) ^c	0.016	0.551
Institution's policy on controlled drinking	2.6 \pm 1.4 ^b	30 (55.6) ³	24 (44.4) ^c	0.003	0.485

^aLogistic regression to investigate specialists' acceptance of CD: specialists' age, profession, school of theory, whether working in an institution, basis of opinion on CD and definition of CD. All tests were two-sided and at a significance level of 5%.

^bMean score on a 5 points-Likert scale \pm SD.

^cData collected on a 5 points-Likert scale, one corresponding to 'do not agree', five to 'fully agree'; percentage calculated for score >3.

(n = 130, n = 210) stated that they practiced treatment aiming at CD for some of their patients.

The most common basis for specialists' opinion on the goal of CD was professional experience of treating alcohol-dependent patients, followed by their school of theory (mean score on a 5-point Likert scale, one corresponding to 'do not agree', five to 'fully agree': 4.0 \pm 1.3 and 3.1 \pm 1.3, respectively; n = 181). Personal experience, scientific research and their institution's policy on CD had less influence on the specialists' basis for accepting CD as a treatment goal; each of these factors scored less than 3 on a 5 points-Likert scale (n = 181) (Table 1).

Table 2 confronts criteria for success used in clinical practice, and criteria expected in published literature. The preferred criterion for success used by respondents in clinical practice was quality of life, whereas 44.8% responded that

they expected the primary endpoint in clinical trials to be 'no lapse'.

One-third of respondents (34%, n = 69, n = 203) considered that at least half of their patients initially request CD as their treatment goal. However, more than half of the specialists who responded (57.2%, n = 119, n = 208) offered CD as a goal for <5% of their patients, while fewer than 5% of specialists initially set CD as a treatment goal for more than a half of their patients (4.8%, n = 10, n = 208).

Patient characteristics that influence specialists' choice of CD as a treatment goal

Table 3 shows the patient characteristics that influenced the specialists' decisions regarding the acceptability of CD as a treatment goal for their patients.

Table 2. Criteria for success used in clinical practice, and criteria expected in published literature

Criteria for successful treatment of alcohol dependence	<i>n</i> (%)
Preferred criterion for success used in clinical practice (<i>n</i> = 216):	
Damage linked to use of alcohol	17 (7.8)
Dependence criteria	15 (6.9)
Abuse criteria	1 (0.5)
Heavy drinking days	0 (0)
Number of drinks per day	1 (0.5)
Number of days of abstinence and number of drinks per day	13 (6.0)
Number of days of abstinence	35 (16.1)
No lapses	5 (2.3)
Quality of life	130 (59.9)
Primary endpoint expected in clinical trials of alcohol dependence (<i>n</i> = 173):	
Damage linked to use of alcohol	31 (17.9)
Dependence criteria	8 (4.6)
Abuse criteria	4 (2.3)
Heavy drinking days	25 (14.5)
Number of drinks per day	1 (0.6)
Number of days of abstinence and number of drinks per day	3 (1.7)
Number of days of abstinence	4 (2.3)
No lapses	77 (44.5)
Quality of life	20 (11.6)

Table 3. Patient characteristics that influenced specialists' choice of CD as a treatment goal

Characteristic	Specialists <i>n</i> (%) <i>n</i> = 93
Patient's desire	82 (88.2)
Perception of self-efficacy	69 (74.2)
Previous relapse	58 (62.4)
Social stability	50 (60.2)
Dependence severity	54 (58.1)
Patient status	34 (36.6)
Physical illness	36 (38.7)
Age	25 (26.9)
Marital status	11 (11.8)

Among specialists who accepted CD as a treatment goal, several patient characteristics (patient's desire, self-efficacy, previous relapse, social stability, dependence severity, residential/ambulatory status, physical comorbidity, age and marital status) influenced the specialists' choice of CD as a goal, with mean scores ranging from 4.5 ± 0.8 to 2.3 ± 1.2 on the 5-point Likert scale. The mean scores for physical comorbidity, age, and marital status were less than 3.

Description of specialists that accepted or rejected CD, and comparison between groups

Table 1 lists the characteristics of specialists who did or did not accept CD as a treatment goal. Age and basis of opinion on CD were independent variables that significantly differed between specialists who either accepted or rejected CD as a treatment goal. Respondents who accepted the goal of CD were younger than those who rejected that goal. Among specialists who accepted the goal of CD, the basis for their opinion of a goal of CD was characterized by higher scores for professional experience and school of theory, and lower scores for scientific research and personal experience. Regarding the difference between groups on the impact of scientific research on the acceptance of CD as a therapeutic target, it was not sustained in multivariate analysis. One

should note the overall low score of this criterion for all responders (mean score on a 5 points-Likert scale: 2.9 ± 1.4).

The group that accepted the goal of CD contained more general practitioners and psychiatrists, and fewer hepatogastroenterologists. The specialists' main school of theory was also significantly different between the two groups ($P = 0.023$, $n = 216$): the group that accepted the goal of CD contained almost twice as many specialists who mainly used cognitive behavioural therapies compared with the group that rejected the goal of CD, whereas the proportion of specialists who used the Twelve Steps approach in the group that rejected the goal of CD was more than ten times that in the group who accepted the goal of CD. Feeling closest to the Twelve Steps theory was significantly associated with non-acceptance of goal of CD ($P = 0.001$).

There was no difference between the two groups with respect to the type of patient recruited for treatment, either in terms of age or substances involved in the addictive behaviour.

Practice setting also differed significantly between groups: few specialists who accepted the goal of CD worked in an institution. Among respondents who were working in an institution, specialists who accepted the goal of CD were over represented in outpatient settings ($P < 0.001$, $n = 180$).

The definition of CD as an outcome was not an independent factor associated with acceptance of the goal of CD, but use of quality of life versus a threshold drinking level to define CD as an outcome was associated with acceptance of the goal of CD ($P < 0.05$). Specialists were then asked what threshold of drinks, expressed as number of drinks per week, they thought might correspond with CD as an outcome; those who rejected goal of CD stated a significantly lower threshold than those who accepted goal of CD (8.2 ± 5.5 vs. 12.7 ± 4.6 for women, and 12.6 ± 8.2 vs. 18.0 ± 7.1 for men, $P < 0.001$ for both comparisons).

DISCUSSION

In our study, nearly half of the French specialists who responded to our questionnaire endorsed CD as a goal for the treatment of alcohol dependence. This finding places France mid-way between countries such as Australia, Britain and Switzerland, where previous studies in 1997, 1992 and 2009, respectively, reported widespread acceptance of CD as a goal, (Rosenberg *et al.*, 1992; Donovan and Heather, 1997; Klingemann and Rosenberg, 2009), and the USA, where acceptance of CD as a goal was reported to be low in 1994 (Rosenberg and Davis, 1994). Our results place France closest to Canada, where acceptance of CD as a goal was rated as intermediate in 1996 (Rosenberg *et al.*, 1996). France is a country with a strong cultural pressure to drink alcohol (particularly wine) on a daily basis, and this tradition has been supported by the importance of wine production to the French economy. However, total alcohol consumption in France has decreased by 50% at the population level since 1970 (INSERM, 2003). Clearly the cultural role of alcohol in France is changing, but nonetheless abstinence from alcohol may be a particularly difficult choice. In our study more than one-third of specialists responded that at least half of their patients initially propose CD as a treatment goal; this result reflects recent findings about initial goals for problem

drinking in the UK (Heather *et al.*, 2010). We noted a gap between initial treatment goals between alcohol specialists and their patients, which may partly be explained by the traditional paternalist attitude of European physicians (Hottot *et al.*, 2001). This lag between acceptance and practice could reflect a discomfort in clinical practice rather than the choice of applying a harm reduction approach. The many comments we received suggest that it could rather be a default attitude on the part of professionals who do not accept this in theory, but have some patients who do not aim for abstinence.

Our study supports the major impact that type of setting has on acceptance of CD as a goal by treatment services, as previously reported (Donovan and Heather, 1997; Rosenberg *et al.*, 1996).

Factors linked to the choice of treatment goals among French alcohol specialists—perceived self-efficacy, severity of dependence, social stability and history of relapse—were consistent with those identified in other countries (Rosenberg *et al.*, 1992; Rosenberg and Davis, 1994). The patient's own desire with respect to the therapeutic goal was considered to be the most important factor, in line with previous suggestions that letting patients choose their goal has an important beneficial impact on treatment outcome (Hodgins, 2005). Our survey did not identify physical illness as an important factor in choice of treatment goal, in contrast with findings from a previous paper that explored the effect of liver damage (Rosenberg and Davis, 1994). However, the apparent difference may be due to the fact that our questionnaire asked about physical illness, which covers a broader field than liver damage.

We identified a number of factors that were independently associated with acceptance of CD as a goal: age; professional background; definition of CD as an outcome, reference to quality of life, and basis of opinion on CD as a goal. These results support earlier findings: for example, the impact of professional experience on acceptance of CD as a goal has previously been described in the UK (Rosenberg *et al.*, 1992). Our study found professional experience to be associated with acceptance of CD as a goal. This may result from the need to experience success with one patient who is aiming for CD, in order to be convinced of the validity of this therapeutic goal, given that aiming for CD is not clearly recognized in French recommendations for the treatment of alcohol dependence. In contrast, relying on personal experience as a basis for opinion on CD as a goal was independently associated with non-acceptance of CD as a goal; this may be due to a desire to share a successful personal goal of abstinence or, on the other hand, by current personal difficulties influencing professional practice. However we did not ask respondents to specify whether the 'personal experience' used to support the opinion of these specialist alcohol workers reflected their own alcohol problem or that of a relative.

Nevertheless, our finding supports other publications which show that treatment of alcohol dependence is influenced not only by scientific data but also by cultural and societal factors (Klingemann and Bergmark, 2006).

Our survey results also revealed a discrepancy between the criteria for success used by alcohol specialists in clinical practice, versus those they expected to see in literature. Quality of life was the most important criterion in clinical practice, but there is no consensus on how it should be

assessed. Development of a specific quality of life scale for use in the field of alcohol dependence would allow treatment specialists to have confidence in trials that include quality of life as a major endpoint. It would also allow comparison of abstinent and non-abstinent goals in a more satisfactory manner.

To our knowledge, this was the first study of the acceptance of CD as a goal among French alcohol specialists. Our sample ($n = 547$) was large compared with previous studies in other countries: 196 services in the USA, 136 in Switzerland, 179 in Australia, 196 in Canada, 180 in the UK (Rosenberg *et al.*, 1992; Rosenberg and Davis, 1994; Rosenberg *et al.*, 1996; Donovan and Heather, 1997; Klingemann and Rosenberg, 2009). The design of our study had some interesting features, as we surveyed alcohol specialists rather than alcohol treatment departments, which were surveyed in other countries. Consequently, in addition to specialists' acceptance of CD as a goal, we also reported their personal opinion and professional characteristics. Several factors that were independently associated with acceptance of CD as a goal were identified, and these may contribute to better understanding of the debate about goal of CD.

Despite the relatively low response rate to the questionnaire (48.1%), our sample was an acceptable representative of SFA members, as it had the same geographical and professional distribution as SFA members overall. In addition, members of the SFA are perhaps not representative of all French specialist alcohol workers, including the fact that some work abroad. Moreover, the status of members remains unclear, because to be a member, being sponsored twice is enough. We do not know the proportion of clinicians and non-clinicians among the members of the SFA, and in the investigation. However, the survey questions are relatively technical and clinically oriented; our impression from some feedback was that non-clinicians were unlikely to respond to the questionnaire.

The response rate also decreases over the questionnaire, probably because of its length, and because responses were made mandatory through the software: this choice has allowed us to limit the amount of missing data, but made the completion of the questionnaire more demanding, and was probably responsible for dropout completing the questionnaire at the time of difficult questions.

Some commentators have cautioned that alcoholism research can have links with the alcohol beverage industry (Babor 2009). Several comments and emails were sent to us, suspecting that we had a relationship to the alcohol industry, reflecting mistrust among some specialist alcohol workers regarding the issue of CD, and this may have been a further lowered response rates.

CONCLUSION

With nearly half of French alcohol specialists stating that they accepted CD as a goal for their patients, France occupies an intermediate position compared with other countries in terms of acceptance of CD as a goal. The main criterion used by French specialists to select a treatment goal is patient preference. Although there is not currently any consensus among French alcohol specialists regarding the

definition of CD as an outcome, quality of life is the most frequently chosen definition, and it is also the main criterion of success in clinical practice. However, quality of life is not currently considered to be a primary endpoint in clinical trials of the treatment of alcohol dependence. The definition of CD as an outcome was independently associated with acceptance of CD as a goal among specialists, as were personal and professional characteristics. The low impact of scientific literature on specialists' opinion raises questions regarding ways to translate research findings into clinical practice in the field of alcohol treatment. Development of specific measurement tools could be one way to increase the impact of research findings on clinical practice.

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Du point de vue du patient (Luquiens et al. 2014)

Définitions

Les trois composantes des soins centrés sur le patients sont: (a) ils assurent au patient d'être invité à participer aux échanges et à la prise de décision concernant ses besoins de santé; (b) ils mettent l'accent sur les objectifs du patient; (c) ils additionnent les savoirs de tous les membres de l'équipe à la connaissance et à la conscience que le patient a de lui-même. Pour l'académie de médecine américaine, adopter une approche centrée sur le patient est l'une des étapes indispensables à l'amélioration de la qualité des soins. Cela correspond à prodiguer des soins dans le respect et l'adéquation avec les préférences des patients, leurs valeurs, et à s'assurer que toutes les décisions sont guidées par les valeurs des patients (Institute_of_medecine 2001). La FDA contribue au développement de la médecine centrée sur le patient, par des initiatives comme le Prescription Drug User Fee Act, dont une des missions est le développement de produits de santé, centrés sur le patient. Le patient est considéré comme premier expert de sa maladie, le plus à même d'évaluer un rapport bénéfice-risque, et d'identifier des besoins non ou mal pris en compte (Mullin 2012). Theresa Mullin souligne que la FDA pourrait bénéficier du recueil systématique du point de vue du patient sur la maladie et sur son impact sur la vie quotidienne, ainsi que sur la manière d'évaluer les différentes options thérapeutiques. L'alliance internationale des organisations de patients a établi comme deuxième point clé de la déclaration des soins centrés sur le patient, le droit et le devoir qu'avaient les patients à être considérés comme partenaires des soins. Cela intègre la nécessité des soins d'être en adéquation avec les besoins des patients dans le but ultime d'atteindre la meilleure qualité de vie possible (International_alliance_of_patients'_organizations 2006).

Application du modèle de médecine centrée sur le patient en alcoologie.

Resituer historiquement l'émergence de la médecine centrée sur le patient permet de donner un éclairage sur les évolutions récentes en alcoologie. Les prémices de la médecine centrée sur le patient ont débuté dans les années 60 par le regroupement de patients comme « the

Independent Living », identifiant le modèle médical paternaliste prédominant , ayant tendance à maintenir la personne malade dans une situation de dépendance (Hayes and Hannold 2007; Patel 2012). Plus tard, dans les années 80, Foucault proposa la théorie selon laquelle le modèle médical paternaliste, par le fait de réserver les connaissances médicales aux spécialistes, contribuerait à conserver une certaine emprise des « sachants » sur les patients et donc une forme de pouvoir imposé (Foucault 1980). Au même moment, les premiers regroupements de patients revendiquaient un partage du pouvoir médical, "empowerment", et la possibilité de participer aux prises de décisions de santé, notamment dans le cadre de l'épidémie de VIH qui faisait rage, en réclamant des mises à disposition rapide de traitements efficaces et en organisant par endroit leur délivrance. Ces changements continuent de faire évoluer les représentations du grand public sur l'organisation des soins et les modèles médicaux, comme l'illustre le film multi-Oscarisé en 2014 « Dallas Buyer Club » de Jean-Marc Vallée. L'Organisation mondiale de la santé note d'ailleurs que les mouvements plus tard renommés de participation des patients ont émergé au sein de populations minoritaires ou stigmatisées (WHO_Europe 2006). Le trouble d'usage d'alcool est une des pathologies les plus stigmatisées (Stuart 2012). C'est probablement l'un des facteurs ayant contribué à la constitution d'associations de personnes ayant ou ayant eu un trouble d'usage d'alcool, s'impliquant particulièrement dans les réflexions récentes sur les objectifs thérapeutiques, ou par exemple en France se traduisant par un certain lobbying ayant conduit l'agence française du médicament à délivrer une recommandation temporaire d'utilisation pour le Baclofène à visée de maintien de l'abstinence ou de réduction de la consommation d'alcool en l'absence d'argument d'un niveau de preuve élevé (ANSM 2014). La prise en compte de la souffrance du patient en adoptant son point de vue paraît donc essentielle au socle de l'alliance thérapeutique, en alcoologie comme dans les autres spécialités médicales. Pourtant, et ce malgré l'importance de l'approche motivationnelle dans la discipline (Aubin, Benyamina et al. 2011; NICE 2011; SFA, ANPAA et al. 2015), il n'est pas toujours apparu comme évident de donner un poids prépondérant au point de vue du patient en alcoologie.

Il semble y avoir un décalage croissant entre les objectifs de consommation requis dans les essais, la pratique clinique et l'objectif du patient pour qui le changement de mode de consommation paraît être un moyen et non une fin. En effet, les critères subjectifs ont été acceptés comme critères secondaires par l'EMA, mais restent non stipulés par la FDA. . Les recommandations de bonne pratique de la Société française d'alcoologie ont tenté une synthèse de ces apparentes contradictions à travers la réponse à la question « Quels sont les objectifs de l'intervention thérapeutique ? » : « D'une certaine façon, l'objectif du traitement d'un mésusage de l'alcool est d'abord l'amélioration de la qualité de vie des personnes. Ainsi, l'intervention thérapeutique devrait, selon la situation particulière du sujet, cibler la santé physique et psychologique, l'adaptation interpersonnelle, sociale et professionnelle, la situation judiciaire, et les autres comportements addictifs et à risque. Cependant, une véritable amélioration de la situation du sujet passe par un changement important de la consommation d'alcool, que ce soit vers l'abstinence ou une réduction de la consommation. C'est pourquoi le traitement cible généralement d'abord ce changement de consommation et sa stabilisation.» (SFA, ANPAA et al. 2015).

L'application du modèle de médecine centrée sur le patient implique donc une réflexion sur les outils de mesure de l'effet thérapeutique (Luquiens and Aubin 2014). Elle implique de favoriser l'auto-évaluation (Robinson, Sobell et al. 2014). Le taux d'essais en alcoologie rapportant des mesures d'auto-évaluation est passé de 89% des essais dans les années 90 à 100% des essais en 2005. Elle implique également la diffusion de l'utilisation de mesures subjectives, notamment l'utilisation d'instruments proches des préoccupations des patients. Les mesures subjectives rapportées par le patient prennent leur essor dans le contexte des soins centrés sur le patient, qui impliquent que le patient participe activement à l'évaluation de son état et de sa situation et aux prises de décisions le concernant. Un « Patient-reported outcome » (PRO) est tout type de rapport du statut d'un patient relatif à sa condition de santé, venant directement du patient, sans interprétation de la réponse du patient par le clinicien ou un autre tiers (FDA 2009). Dans un essai clinique, un PRO peut être utilisé pour

mesurer l'effet d'une intervention thérapeutique sur un ou plusieurs concepts. L'utilisation d'un PRO est conseillée pour mesurer un concept que le patient est le plus à même de mesurer ou qui serait mieux mesuré de la perspective du patient. Ils concernent généralement les symptômes, signes ou aspects du fonctionnement directement reliés au statut de la maladie. Ils ne sont jamais la mesure d'un effet physiologique. S'ils sont destinés à mesurer l'effet d'un traitement sur la maladie elle-même, ils peuvent être le recueil de symptômes, de signes ou de performance physique, mais pas être un examen physique. S'ils sont destinés à mesurer l'effet d'un traitement sur les symptômes associés à une maladie, ils peuvent être un score de symptômes, l'estimation d'une performance physique ou de limitations physiques liées à la maladie. Les PRO doivent pour leur développement faire participer de façon extensive les patients à la génération des items, afin d'assurer la pertinence du contenu de ce qui est mesuré, du point de vue du patient (FDA 2009). Sans la documentation adéquate de la contribution des patients, la validité de contenu d'un PRO doit être questionnée. Comme on va le voir, nombre mesures rapportées par les patients et utilisées en alcoologie ne sont pas en adéquation avec ces principes.

Entre 1980 et 1984, le pourcentage d'études portant sur le traitement de l'alcool et renseignant au moins un critère en dehors des quantités d'alcool ou de la notion d'abstinence, était de 60.4%, alors qu'il était passé à 82.0% entre 1989 et 1993 (FDA 2015). Ces domaines étaient répertoriés en : domaine professionnel, ré-hospitalisations liées à l'alcool, santé physique, tests psychologiques, domaine social, domaine familial, traitement complémentaire, arrestations dues à l'alcool, logement, domaine interpersonnel, fonctions cognitives, domaine légal, émotions, mesures globales, mortalité. Si on s'intéresse aux critères subjectifs non relatifs aux quantités consommées d'alcool (hors hospitalisations, arrestations par exemple), seuls 56% des essais récents rapportent ce genre de mesure (Robinson, Sobell et al. 2014). On retrouve des mesures interrogeant plusieurs domaines:

- l'inventaire des conséquences négatives liées aux consommations d'alcool. L'échelle *Drinker Inventory of Consequences* »)(Miller and Longabaugh 1995), issu du projet MATCH,

permet de faire cet inventaire par un auto-questionnaire de 45 items. Ces items ont été générés par les experts.

- la sévérité du trouble. Elle peut être mesurée par des instruments génériques, comme la Clinical Global Impression scale – severity (Busner and Targum 2007), ou des instruments plus spécifiques de l'addiction, comme l' « addiction severity index », ou de la dépendance à l'alcool, comme « Alcohol Dependence Scale» (Skinner and Allen 1982). On peut aussi mesurer l'amélioration clinique selon le clinicien, comme la « Clinical Global Impression scale - improvment » (Busner and Targum 2007). Certains auteurs ont proposé récemment d'utiliser des critères diagnostiques comme les critères du DSM-5 de façon dimensionnelle et non catégorielle, pour obtenir un score de sévérité, allant de 0 à 11 (Fazzino, Rose et al. 2015).

- l'alliance thérapeutique. Elle peut être explorée du point de vue de l'expert par le clinicien lui-même, par exemple par le « Working Alliance Inventory » - clinician part et « Working Alliance Inventory » -patient part, qui a été utilisé dans l'essai COMBINE (Anton, O'Malley et al. 2006). Ces deux parties de l'échelle peuvent être comparées pour mesurer la cohérence de cette évaluation.

- la satisfaction du patient, qui peut être mesurée par la « Patient satisfaction for Medical Management», utilisée également dans l'essai COMBINE (Ernst, Pettinati et al. 2008). Dans cet essai, il est intéressant de noter que l'alliance thérapeutique était associée au nombre de jours d'abstinence et à la réduction du nombre de jours de consommations excessives, mais que la satisfaction des patients vis-à-vis de leur prise en charge médicale était associée au nombre de jours d'abstinence mais pas à la réduction du nombre de jours de consommations excessives. La satisfaction du patient vis-à-vis de sa prise en charge ne correspond donc pas toujours à son évolution, mais peut aussi plutôt refléter une discordance dans les objectifs de départ entre le patient et le clinicien.

- le nombre de perdus de vue dans les essais, qui reflète selon les interprétations, l'alliance thérapeutique, l'efficacité ou l'acceptabilité des interventions.

- la mesure subjective de l'efficacité du traitement par le patient. Elle peut être mesurée par un auto-questionnaire simple, comme le « Treatment effectiveness assessment » (Ling, Farabee et al. 2012), rassemblant 4 items (usage de la substance, conditions de vie, santé et relations interpersonnelles). Cette mesure est présentée comme un instrument centré sur le patient, mais là encore les domaines ont été choisis par les experts, s'appuyant sur les priorités recensées par le « Substance Abuse and Mental Health Services Administration » pour définir la rémission.

- les pensées obsédantes et compulsions à consommer de l'alcool, mesurées par l'Obsessive Compulsive Drinking Scale (OCDS) (Anton, Moak et al. 1995), un auto-questionnaire dérivé du Yale-Brown Obsessive Compulsive Scale -heavy drinkers, lui-même un hétéroquestionnaire développé du point de vue d'experts. L'OCDS a été montré comme n'étant que peu corrélé aux critères de consommation, et mesurant donc une autre dimension de l'alcoolodépendance.

- les envies irrésistibles de consommer, aussi appelées « craving » et les urgences à consommer. On distingue classiquement trois types de craving, le craving de récompense, le craving de soulagement, et le craving obsessionnel. Plusieurs instruments permettent d'évaluer ce concept, dans sa multi-dimensionnalité. On trouve notamment l'« Alcohol Craving Questionnaire » (Singleton, Tiffany et al. 1995), le « Craving Typology Questionnaire ». Certains instruments tentent de mesurer la fréquence et le caractère intrusif des envies. Une des difficultés dans la mesure du craving est qu'il peut être très changeant même sur une période de courte durée, et son évaluation semble optimisée par l'utilisation de mesures répétées en temps réel sur dispositifs mobiles comme les smartphones.

- la qualité de vie. Les instruments de mesure seront détaillés dans le chapitre suivant.

Les derniers éléments ont été développés dans la publication ci-dessous: Luquiens, A. and H. J. Aubin (2014). "Patient preferences and perspectives regarding reducing alcohol consumption: role of nalmefene." Patient Prefer Adherence 8: 1347-52. (Luquiens and Aubin 2014).

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

This article was published in the following Dove Press journal:
Patient Preference and Adherence
29 September 2014
[Number of times this article has been viewed](#)

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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.^{1,2} Alcohol consumption is estimated to be responsible for 3.8% of all deaths.³ The global costs of excessive drinking are estimated to exceed \$200 billion a year.³ 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.^{4,5} 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.⁵ 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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<http://dx.doi.org/10.2147/PPA.S57358>

Patient Preference and Adherence 2014:8 1347–1352

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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.⁶

The main limiting factor for access to care in alcohol use disorder appears to be the reluctance to engage in abstinence.⁷ In fact, the majority of patients seem to initially aim for a reduction in consumption.^{8,9} A reduction in consumption is not proposed everywhere to the same extent to patients entering treatment,⁸ 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.⁸ 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.^{3,10} 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.¹¹

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,¹² 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.¹³ 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.¹⁴

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.^{15,16} 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.¹⁷ 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.¹⁸ 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.¹⁹ However, returning to the pre-morbid state is a usual demand from patients suffering from any illness.²⁰ It should not be surprising that patients with alcohol use disorder also ask for this return to their pre-morbid 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.¹⁹ Nonadherence to life-style modification is a common feature of other chronic illnesses, for instance, among diabetic patients,²¹ 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.²²

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 enhancement²³ 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.²⁴

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%.²⁵ 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,²⁶ craving,^{27,28} and health-related quality of life (HRQOL).²⁹ 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.³⁰ 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.³¹ Craving is believed to be the consequence of a complex neurobiological dysfunction, and it is now conceived as a therapeutic target itself.³² Patient satisfaction has been poorly explored in the alcohol use disorder field.³³ 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.³⁴ 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.^{35,36}

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.³⁷ 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.³⁸ 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.³⁹ 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.⁴⁰ 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.⁴¹ 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 nalmefene⁴² 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 μ , δ , and κ receptor profile. In vitro studies have demonstrated that Nalmefene is a selective opioid receptor ligand with antagonist activity at the μ and δ receptors and partial agonist activity at the κ receptor. In vivo studies have demonstrated that nalmefene reduces alcohol consumption, possibly by modulating cortico-mesolimbic functions.¹⁰ 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 ; $P=0.012$).⁴³ 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.⁴⁴ 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 6.³⁵ 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 ; $P=0.036$).⁴⁵ 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.⁴² 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.⁴⁶

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.⁴⁴ The treatment-emergent adverse events that led most-commonly to discontinuation (occurring in $\geq 2\%$ of nalmefene recipients) included dizziness, nausea, fatigue, and headache.⁴⁴

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.⁴⁷ One should keep in mind that either abstinence or alcohol reduction are merely means to attain the therapeutic goal.

Disclosures

AL has received a travel grant to attend a scientific meeting from Lundbeck. HJA has received sponsorship to attend scientific meetings, speaker honoraria, and consultancy fees from Bioprojet, D&A Pharma, Ethypharm, Lundbeck, Merck-Serono, Novartis, and Pfizer. The authors report no other conflicts of interest in this work.

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Qualité de vie – définitions

La qualité de vie correspond au ressenti et saisi du vécu du patient sur différents domaines de fonctionnement. Elle n'est classiquement pas reflétée par des mesures évaluant des symptômes (Carr, Gibson et al. 2001). On distingue deux types de mesures de la qualité de vie (Aaronson 1988) :

- i. la qualité de vie globale, non liée à la santé, qui constitue une évaluation de sa qualité de vie par rapport à un idéal propre à chacun. L'Organisation Mondiale de la Santé l'a définie en 1993 comme « la perception qu'un individu a de sa place dans la vie, dans le contexte de la culture et du système de valeurs dans lequel il vit, en relation avec ses objectifs, ses attentes, ses normes et ses inquiétudes. ». Elle constitue en théorie la mesure de l'écart entre l'état actuel et un idéal propre à chacun. Elle est difficile à mesurer puisqu'elle a pour ambition de saisir le degré d'accomplissement des besoins et désirs communs au plus grand nombre. Elle est réputée peu sensible au changement (Leplege 2011). En pratique il n'est donc pas recommandé de l'utiliser pour mesurer l'efficacité d'un traitement (EMEA 2005). La mesure la plus consensuelle a été développée par l'organisation mondiale de la santé, la World Health Organization Quality of Life scale (WHOQOL) .
- ii. la qualité de vie liée à la santé (QVLS), réputée plus robuste et plus sensible au changement, qui interroge la perception qu'a un patient de l'impact d'une maladie en particulier. Les domaines de la vie classiquement explorés dans la QVLS sont (1) l'état physique, incluant l'autonomie et les capacités physiques (2) le bien-être physique, incluant la douleur et les symptômes physiques (3) l'état psychologique, incluant l'anxiété et la dépression, et (4) les relations sociales, incluant les relations à la famille, aux amis et le travail. Les instruments génériques explorent ces domaines sans prise en compte des spécificités d'une pathologie en particulier, et peuvent ainsi être utilisés en théorie dans n'importe quelle pathologie. Les instruments spécifiques,

eux, tentent de mesurer les spécificités de l'impact sur la qualité de vie d'une pathologie en particulier.

Les mesures génériques les plus utilisées de QVLS ont été développées initialement pour des pathologies cardiovasculaires (MOS-SF-36) (Ware and Sherbourne 1992) ou dans une optique de traduction en score d'utilité médico-économique et de comparaison entre les pathologies (EuroQolGroup 1990). La qualité de vie permet ainsi de quantifier le coût efficacité des interventions, par l'utilisation d'algorithmes à partir de l'échelle EQ5D par exemple, permettant d'attribuer une valeur monétaire à l'amélioration de la qualité de vie mesurée (Laramee, Brodtkorb et al. 2014).

L'utilisation exponentielle de ce concept est illustrée par le nombre d'articles référencés correspondant au mot clé "qualité de vie" sur l'Index Medicus, de 90 dans les années 70, montant à 7000 en 2003 (Donovan, Mattson et al. 2005), atteignant 212631 sur Medline en 2015 (site ayant pris le relais de l'Index Medicus en 2004). Cet accroissement est bien sûr à discuter en tenant compte de l'accroissement global des références. Pour comparaison, le mot clé "alcohol dependence" correspondait à 254 articles pour l'année 2000 et 596 pour l'année 2014 (X 2.3), alors que le mot clé "qualité de vie" correspondait à 5189 articles en 2000 et à 18395 articles en 2014 (X 3.5).

Parmi les premiers champs à s'être saisi de ce genre de mesure on retrouve les troubles cardiovasculaires (Kaplan 1988) et la cancérologie, pour qui les domaines de la vie cités ci-dessus sont particulièrement pertinents (Aaronson 1988). Pourtant, on a retrouvé chez les patients les plus sévères un phénomène de "response shift", c'est à dire que les patients ayant atteint un niveau de qualité de vie particulièrement dégradé semble se satisfaire dans une plus grande mesure d'une amélioration même minime, et estime leur qualité de vie à un meilleur niveau que d'autres patients n'ayant jamais atteint une dégradation aussi considérable de leur qualité de vie (Schwartz, Ahmed et al. 2013). Ce phénomène est bien sûr gênant pour évaluer l'efficacité thérapeutique.

La mesure de la qualité de vie est nécessairement rapportée par le patient puisqu'il s'agit de mesurer le vécu subjectif de celui-ci. Pourtant, contrairement aux principes recommandés par la FDA pour le développement des PRO, les items de ces deux échelles ont été générés par des experts, sans participation des patients. En alcoologie, il s'agit d'un point particulièrement sensible. Dans le contexte de stigmatisation, y compris au sein du corps soignant (Ronzani, Higgins-Biddle et al. 2009), du trouble d'usage d'alcool, la détermination par les experts des domaines de la vie impactés par les consommations d'alcool se rapproche d'un recensement de conséquences négatives liées aux consommations, comme une liste d'évènements qui n'aurait plus rien de subjectif, et pour lesquels l'impact sur la qualité de vie ne serait finalement pas saisi (Miller and Longabaugh 1995).

On considère que la qualité de vie est très impactée dans le trouble d'usage d'alcool, qu'il s'agisse de la qualité de vie globale ou liée à la santé (Donovan, Mattson et al. 2005). Cet impact est retrouvé dans d'autres addictions (Zubaran and Foresti 2009). Il a été montré avec des échelles génériques que la sévérité du trouble d'usage d'alcool était associée à la détérioration de la qualité de vie (Daepfen, Krieg et al. 1998), et, dans un essai ouvert, que les patients ayant la période d'abstinence la plus prolongée semblaient être ceux qui récupéraient une meilleure qualité de vie, qui devenait alors au bout de six mois comparable à la qualité de vie de la population générale (Morgan, Landron et al. 2004). Ces résultats ont été remis en cause par des données récentes ayant réévalué à distance la qualité de vie globale (c'est à dire non liée à la santé) des patients ayant bénéficié d'un essai thérapeutique 7 ans auparavant. Les patients ayant réduit leur consommation avaient autant amélioré leur qualité de vie que ceux étant devenus abstinents (Frischknecht, Sabo et al. 2013). L'évolution à 3 ans des patients présentant un trouble d'usage d'alcool de la cohorte National Epidemiologic Survey on Alcohol and Related Conditions a également retrouvé une récupération similaire voire meilleure de la qualité de vie chez les patients non-abstinents ayant réduit leur consommation par rapport aux abstinents (Dawson, Li et al. 2009). Ces résultats soulèvent là encore la question de la pertinence clinique de certains critères relatifs

à la consommation d'alcool. De plus, la réévaluation très à distance des patients dans ces deux études pose aussi la question de la temporalité pour évaluer une amélioration de la qualité de vie. Il n'existait pas jusqu'au présent d'échelle spécifiquement développée pour saisir l'impact des consommations d'alcool sur la qualité de vie. La seule échelle spécifique recensée était une version réduite de la SF-36, l'Alcohol Quality of life – 9 items, qui ne mesurait donc rien de plus que la SF-36, une échelle générique. Devant le grand nombre d'échelles spécifiques dans d'autres champs s'étant multiplié ces dernières années, et le risque de développer un instrument qui se verrait peu utilisé ou de disperser les données, l'agence européenne du médicament a rédigé des recommandations pour la mesure et le développement d'instrument de QVLS. Ces recommandations stipulent que tout nouveau développement d'un instrument doit être justifié par l'absence d'instrument mesurant la qualité de vie dans la champ en question et la pertinence réelle d'un instrument spécifique (EMA 2005).

Objectifs de la thèse

Les objectifs de cette thèse sont multiples. Il s'agit principalement de:

- Faire l'état des lieux et décrire l'évaluation de la qualité de vie comme mesure de l'efficacité d'une intervention en alcoologie
- Définir le besoin de développement d'une nouvelle mesure rapportée par le patient de la qualité de vie spécifique au trouble d'usage d'alcool
- Développer cet instrument en adoptant une méthodologie centrée sur le patient
- Valider cet instrument dans différentes populations cibles et renseigner les propriétés psychométriques de cet instrument

Qualité de vie liée à la santé en alcoologie : état des lieux - "Quality of life among alcohol-dependent patients: How satisfactory are the available instruments? A systematic review " (Luquiens et al. 2012)

L'article « Luquiens, A., M. Reynaud, et al. (2012). "Quality of life among alcohol-dependent patients: how satisfactory are the available instruments? A systematic review." Drug Alcohol Depend 125(3): 192-202. » publié en anglais est ici synthétisé en français, puis inséré dans sa version complète en anglais.

Pour répondre au premier objectif de cette thèse, il paraissait important de pouvoir faire une revue systématique des essais cliniques ayant rapporté des résultats sur l'efficacité d'une intervention sur la qualité de vie chez les patients alcoolodépendants. Nous avons comme objectif d'identifier les instruments existants et déjà utilisés dans cette population, et de la comparer aussi bien dans leur contenu que dans leur capacité à saisir le changement chez ces patients.

Méthodes:

Nous avons mené une recherche sur bases PubMed/MEDLINE, EMBASE et PsycINFO. Les termes suivants ont été combinés pour constituer les mots clés d'intérêt: "alcohol dépendence" ou "alcohol abuse" ou "alcohol use disorder" ET "trial" ET "quality of life". Les critères d'inclusion pour les essais étaient: (1) essai randomisé contrôlé visant à améliorer la qualité de vie de patients alcoolodépendants comme critère de jugement primaire ou secondaire, (2) utilisation d'un instrument désigné par les auteurs comme mesurant la qualité de vie. Les critères d'exclusion étaient: (1) les essais ne couvrant que le sevrage d'alcool (2) les essais pour lesquels la population n'était pas alcoolodépendante. Au total nous avons recensé et examiné 331 articles et exclu 313 articles. Dix-huit essais publiés entre 1990 et

2012 ont pu être inclus, utilisant 8 instruments différents pour mesurer la qualité de vie. Pour chaque essai nous avons décrit les instruments utilisés pour mesurer la qualité de vie, le design de l'étude, notamment le but de l'étude, la population, l'intervention testée, la durée du suivi et si la qualité de vie était un critère principal ou secondaire. Nous avons également proposé une analyse décrivant la qualité méthodologique des essais suivant le "Cochrane collaboration tool for assessing risk of bias". Puis nous avons mené une analyse qualitative des instruments mesurant la qualité de vie identifiés, et extrait les domaines de la vie interrogés par ces instruments.

Résultats

Nous avons inclus 18 essais entre 1999 et 2012. La qualité des essais était globalement bonne, même si la majorité n'étaient pas en double aveugle du fait d'intervention de type psychothérapie. Nous avons identifié 8 instruments désignés comme mesurant la qualité de vie par les auteurs de l'essai: the Alcohol Problems Questionnaire (APQ) (Drummond and Ghodse 1999), Medical Outcomes Study 36-Item Short-Form Health Survey version 1 or 2 (SF-36) (Ware and Sherbourne 1992; McHorney, Ware et al. 1993) or 12-Item Short-Form Health Survey (SF-12) (Ware, Kosinski et al. 1996)), the World Health Organization Quality of Life Assessment Instrument (WHO-QOL-26) (WHOQOL 1996), the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (Endicott, Nee et al. 1993), the European Quality of Life Questionnaire (EQ-5D) (EuroQolGroup 1990), the Koskenvuo Quality of Life Scale (Koskenvuo 1979), the Visual Analog Scale on quality of life (VAS) (Scott and Huskisson 1976), and the Treatment of Mild Hypertension Study Health and Well-being Scale (TOMHS-HWBS) (Stamler, Prineas et al. 1987). Tous ces instruments étaient des auto-questionnaires. Contrairement à ce qui était annoncé par les auteurs, les échelles utilisées n'étaient pas toutes sensées mesurer la qualité de vie; par exemple, l'APQ est une échelle recensant les problèmes liés aux consommations d'alcool. Les deux instruments les plus souvent utilisés étaient la SF-36 et ses dérivées (9 fois) et l'EQ-5D (4 fois). Tous les deux sont des instruments génériques reportant la QVLS. La SF-36 a été conçue pour une

étude observationnelle débutée en 1986 chez des patients ayant des troubles cardiovasculaires. Il s'agit d'une échelle à 36 items, comprenant 8 dimensions: le fonctionnement physique, la limitation du rôle physique, la limitation dans le rôle émotionnel, la douleur physique, la santé mentale, le fonctionnement social, la vitalité, la perception générale de la santé. On peut également calculer deux sous-scores: le sous-score mental et le sous-score physique. La SF-36 possède de bonnes propriétés psychométriques en population générale, et a été validée chez les alcoolodépendants (Daeppen, Krieg et al. 1998). L'EQ-5D comprend 5 dimensions: la mobilité, prendre soin de soi, les activités habituelles, la douleur, l'anxiété/dépression. Chaque dimension comprend 3 niveaux, et il en résulte un total de 243 états de santé uniques. Elle possède de bonnes propriétés psychométriques en population générale, mais semblerait peu propice à discerner des différences petites à modérées d'état de santé. Chez les alcoolodépendants, elle présenterait une faible sensibilité au changement (Gunther, Roick et al. 2007).

Le point soulevant le plus de question était la différence non significative entre les groupes pour la qualité de vie pour 4 essais pour lesquels le critère principal montrait une différence significative; ces essais utilisaient l'APQ, la SF-36, l'échelle de Koskenvuo, une échelle visuelle analogique et l'EQ-5D. Le sous-score mental de la SF-36 semblait plus sensible au changement que le sous-score physique.

Nous avons recensés 27 domaines explorés par les instruments utilisés. Ces domaines ont été regroupés en 8 catégories: les relations avec les autres, les activités, l'état physique, l'état psychologique, les difficultés financières, les soins médicaux, les problèmes légaux, la satisfaction avec la vie. Le bien être psychologique était exploré dans 7 instruments sur 8, et la perte d'autonomie physique dans 6 des 8 instruments.

La dispersion des instruments utilisés dans des essais cliniques était importante et correspondait à la dispersion décrite par Donovan dans une revue des instruments réalisée en 2005 et utilisés dans des études observationnelles. Notre revue et celle de Donovan ont

donc permis d'identifier 25 instruments différents mesurant la qualité de vie utilisés chez des personnes présentant un trouble d'usage d'alcool, rendant les comparaisons entre études très difficiles. Aucun de ces instruments n'a été développé spécifiquement pour le trouble d'usage d'alcool. La tournure des consignes des instruments de QVLS, ne fait donc jamais référence au rôle de l'alcool sur le domaine exploré, mais le plus souvent à "la santé", pouvant potentiellement rendre difficile l'exploration du domaine en question si le patient fait une différence entre son état de santé et l'alcool en tant que maladie. On sait d'ailleurs que le trouble d'usage d'alcool, comme les autres addictions, est marqué par une tendance forte des patients à l'auto-stigmatisation (Livingston, Milne et al. 2012). L'auto-stigmatisation est définie par le fait de se sentir responsable de sa maladie ou de son état. Les patients ayant cette tendance pourraient avoir plus de mal à compléter une échelle générique de qualité de vie ne mentionnant pas directement l'alcool, considérant que ce qui est interrogé ne concerne pas l'impact de l'alcool. De plus, aucun de ces instruments que nous avons recensés n'a impliqué la contribution de patients dans son développement et la génération des items, et ne respecte donc les recommandations actuelles en matière de mesure de type PRO.

Un seul essai a pu montrer une différence significative de qualité de vie entre les groupes après l'intervention, et la qualité de vie était le critère principal de cet essai. L'absence de différence de qualité de vie mise en évidence dans 4 essais positifs pour le critère principal pourrait s'expliquer par le design inadapté de ses essais pour mesurer la qualité de vie (nombre de sujet, durée), par la faible sensibilité au changement des mesures utilisées dans cette population, ou par le manque de spécificité des instruments utilisés dans le trouble d'usage d'alcool.

Discussion

Cette revue systématique a permis d'identifier le besoin de développement d'un instrument mesure la QVLS spécifique aux patients présentant un trouble d'usage d'alcool, de type PRO

et centré sur le patient, c'est-à-dire respectant les recommandations actuelles de contribution du patient dans son développement.



Contents lists available at SciVerse ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcddep



Quality of life among alcohol-dependent patients: How satisfactory are the available instruments? A systematic review

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ARTICLE INFO

Article history:

Received 7 February 2012
Received in revised form 10 August 2012
Accepted 11 August 2012
Available online xxx

Keywords:

Quality of life
Alcohol dependence
Clinical trials
Systematic review

ABSTRACT

Aim: The purpose of this systematic review was to compare quality-of-life instruments used as outcome measures in randomized clinical trials for alcohol-dependence treatment.

Methods: Randomized controlled clinical trials, indexed in the EMBASE, PubMed and PsycINFO databases since 1981, which aimed at improving the quality of life in alcohol-dependent patients and used as instrument to measure the quality of life, as specifically designated by the authors, were included.

Results: Of the 331 articles screened, 18 studies were included in the review. Eight different quality-of-life instruments were used as outcome measures. Twenty-seven life domains were explored. Between-scale heterogeneity was high. The scale most frequently used was the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36). Only 1 clinical trial demonstrated a significant difference between intervention groups at all endpoints, using the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).

Conclusion: Because many different instruments were used, it is difficult to compare quality-of-life improvement between trials. The most frequently used instrument was a generic health status measure that may not be well suited as a quality-of-life measure for subjects with alcohol dependence. The construction and validation of a specific patient-reported outcome based on alcohol-dependent patients' concerns would effectively contribute to the assessment of treatment efficacy.

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1. Introduction

Therapeutic goals for alcohol dependence are no longer limited to complete abstinence (EMEA, 2010). The forthcoming fifth

edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (<http://www.dsm5.org/ProposedRevision/Pages/SubstanceUseandAddictiveDisorders.aspx>) introduces a diagnostic shift from the binary diagnostic criteria of alcohol dependence and alcohol abuse to a single continuum of alcohol use disorders and introduces a clear measure of severity to help tailor treatment goals. Accordingly, alcohol reduction strategies offer a clear opportunity to address patient heterogeneity and lower the treatment barrier

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by introducing patients to treatment who would otherwise not be treated.

The primary endpoints typically used in clinical trials are based on the quantity of alcohol consumed or counting the number or percentage of days of abstinence or excessive drinking (Allen, 2003). These criteria do not reflect the changes observed in more complex patients who do not have a linear course of their disease or who change their drinking patterns over time (Zywiak et al., 2011). Additionally, these criteria are not directly relevant to clinical practice; they have been shown to be the preferred criteria for success in clinical practice for only a quarter of alcohol treatment specialists (Luquiens et al., 2011). Alcohol use disorders are complex diseases affecting medical, psychological and social domains (Alcohol and Public Policy Group, 2010). How can we show that a therapeutic intervention benefits alcohol-dependent patients regarding this complexity? Many judgment criteria can be used, developed and combined (Cisler and Zweben, 1999; LoCastro et al., 2009), such as: general health, severity of dependence, cost of interventions, negative consequences related to consumption (Miller, 1995) and quality of life (QoL).

QoL describes patients' feelings about domains of functioning that are important to them but that are not captured by traditional symptom assessments (Carr et al., 2001). Traditionally, two types of QoL assessment instruments are distinguished: Health-related QoL and general QoL instruments. Health-related QoL instruments explore patients' perceptions of the impact of a particular disease on their lives. Classically, Health-related QoL involves four domains: (1) physical state, including autonomy and physical abilities; (2) physical well being, including pain and physical symptoms; (3) psychological state, including anxiety and depression; and (4) social relationships including the domains of family, friends and work (Leplège, 1999). General QoL instruments explore overall quality of life independently of any health condition. Their challenging purpose is to capture an overall state of well being, defined as the satisfaction of needs and desires common to most people (Leplège, 1999). This type of QoL instrument is thought to be less robust than health-related QoL instruments. QoL has been investigated in numerous studies in patients with alcohol dependence; however, there is no consensus on the definition of QoL (Zubaran and Foresti, 2009), especially within the field of alcohol use disorder treatment.

Therefore, the instruments used in these studies vary in structure and in the domains they explore. A previous review (Zubaran and Foresti, 2009) investigated QoL in a broader context of substance use. That review found only one instrument that was specifically validated for alcohol-dependent patients: the ALQoL-9, which was directly derived from the generic instrument SF-36. However, its development consisted in an item restriction from the SF-36 which captures the same information as the full-length version but with only nine items and that has been validated in an alcohol-dependent population.

In another review, the relationship between QoL and drinking behavior, alcohol use disorders and treatment outcomes were investigated (Donovan et al., 2005). That review supported the integration of QoL as an outcome measure in alcoholism treatment research. Because of the growing interest in this concept, many studies have been conducted since this review. Although QoL in patients with alcohol dependence may now be considered relevant, the reliability, content and sensitivity to change of the QoL measurements are still sensitive issues that lack data.

A working inventory of the data available in clinical trials seemed necessary before proposing a new specific instrument. Our article is a review of the clinical trials of alcohol-dependent patients that explicitly claim providing a QoL measure as defined by the authors. We decided to include trials even if their instruments were not initially conceived as QoL measures. Our purpose was

to evaluate the current representation of QoL in the alcohol-dependent field, taking into account confusion of concepts. The purpose of this review is to identify the instruments used in clinical trials and to measure changes in QoL post intervention in alcohol-dependent patients. We focused our research on randomized clinical trials (RCTs) to be able to discuss the responsiveness of these measures. We describe the instruments and identify the domains we explored. Our intention was to clarify the concept of QoL as assessed in randomized control trials (RCTs) involving alcohol-dependent patients. Although a comparison of the trials was hindered by the variety of instruments used, we reported the QoL outcomes for each study. This review aimed to guide the choice of an instrument to assess QoL in alcohol-dependent patients and to suggest ways to build a useful, effective, alternative instrument to report changes in QoL experienced by alcohol-dependent patients during treatment.

2. Methods

2.1. Selection of articles

A comprehensive search of the PubMed/MEDLINE, EMBASE, and PsycINFO databases was conducted. The following terms were entered and combined as keywords "alcohol dependence" or "alcohol abuse" or "alcohol use disorder", "trial", and "quality of life". Reference lists of the retrieved articles were carefully screened. Inclusion criteria for the trials were as follows: (1) randomized controlled clinical trials aiming at improving QoL in alcohol-dependent patients as a primary or secondary outcome; (2) articles using an instrument designated explicitly as measuring QoL by the authors as an outcome. Exclusion criteria were the following: (1) articles covering only alcohol withdrawal, a period when QoL could be selectively worsened by acute physical and psychological symptoms specific to withdrawal and not to overall dependence; (2) trials among subjects who did not fulfill alcohol-dependence criteria, even if they had problems with alcohol consumption. We chose to focus on alcohol-dependent subjects who are considered to be the most impacted by their alcohol consumption and who are therefore those with potentially the most significant possible improvement of QoL. We first screened the target population and then the study design. Exclusion explanations respect this order of screening. There was no language restriction except for one article, which was written in Chinese, with no email to contact the authors to obtain more information. All articles were included if published before May 2012. The earliest date of an included study was 1981 in Pubmed and 1993 in PsycINFO and EMBASE. The selection of articles was double-checked. The flow chart presented in Fig. 1 shows the reasons for excluding articles. A total of 331 articles were retrieved, but 313 of these were excluded mainly due to populations or designs that did not fit with our criteria.

Eighteen studies published between 1999 and 2012 met the inclusion criteria and used a total of eight instruments to measure QoL. For each study, we reported the instruments used to assess QoL, the design, including study purpose, the population, the intervention, the length, and whether QoL was a primary or secondary outcome. We also detailed the nature of primary outcome and whether it was able to show a significant difference between groups. We propose a quality analysis of the included trials following the "Cochrane Collaboration's tool for assessing risk of bias" (Higgins et al., 2011), which includes five risks of bias: (1) selection bias, assessing random sequence generation and allocation concealment; (2) performance bias, assessing blinding of participants and personnel; (3) detection bias, assessing blinding of outcome assessment; (4) attrition bias, exploring for incomplete outcome data; and (5) reporting bias, searching for selective reporting.

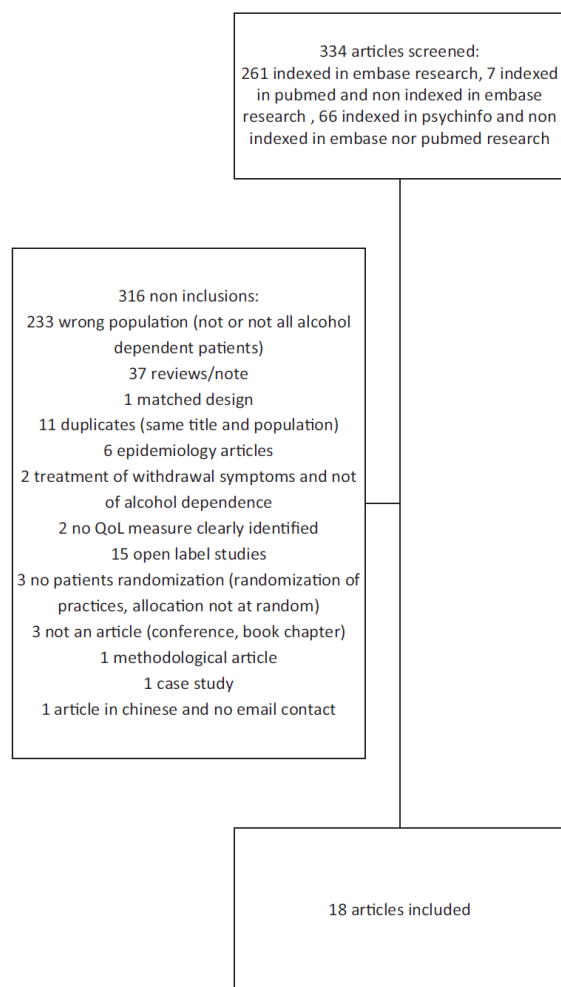


Fig. 1. Flow chart.

3. Results

3.1. Clinical trials and instruments characteristics

We included 18 articles from 1999 to 2012. We identified the following 8 so-called quality-of-life instruments (Table 1): the Alcohol Problems Questionnaire (APQ; Drummond, 1990), Medical Outcomes Study 36-Item Short-Form Health Survey version 1 or 2 (SF-36; McHorney et al., 1993; Ware, 2000) or 12-Item Short-Form Health Survey (SF-12; Ware et al., 1996), the World Health Organization Quality of Life Assessment Instrument (WHO-QOL-26; Szabo et al., 1996), the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott et al., 1993), the European Quality of Life Questionnaire (EQ-5D; The EuroQol Group, 1990), the Koskenvuo Quality of Life Scale (Koskenvuo, 1979), the Visual Analog Scale on quality of life (VAS; Scott et al., 1976), and the Treatment of Mild Hypertension Study Health and Well-being Scale (TOMHS-HWBS; Stamler et al., 1987). All instruments were self-administered.

We assessed the quality of the trials using the “Cochrane Collaboration’s tool for assessing risk of bias” (Table 2). The methodological quality of the studies was globally sound. Ten out of eighteen articles were not double blind, mostly because of implications of psychotherapeutic interventions. Attrition bias due to the handling of incomplete data was found in four trials. In five trials, there was no information about the generation of a randomized sequence.

Contrary to what may suggest their use as QoL instruments, these scales were initially designed for various purposes and referred to different concepts. The first concept is problems related to substance use. The APQ was designed as a clinical instrument for measuring alcohol-related problems. It consists of 11 questions on physical and mental health, problems at work, at home and with the police. The total score ranges from 11 to 22; the higher score indicates a better outcome. It has been used to study the relationship between alcohol-related problems and dependence within the bi-axial model (Williams and Drummond, 1994). Its reliability has been considered as sound among alcohol-dependent patients (Williams and Drummond, 1994), and its relationship with the SF-36 explored; alcohol-dependent patients with no alcohol problems seem to report higher SF-36 scores (Patience et al., 1997). The SF-36, SF-12, EQ-5D and TOMHS-HWBS were constructed to measure health-related QoL; concepts measured in these instruments refer to levels of physical, psychological and social functioning. The SF-36 comes from the Medical Outcome Study (Ware and Sherbourne, 1992), an observational study that was begun in 1986 among subjects with cardiac impairment. It is a 36-item questionnaire and includes eight dimensions: physical functioning, physical role limitation, emotional role limitation, bodily pain, mental health, social functioning, vitality and general health perception. It also includes two sub-scores: the mental and the physical sub-scores. The SF-36 presents good psychometrics properties in a general population, with a Cronbach coefficient greater than 0.85 (Brazier et al., 1992). It has been validated among 147 alcohol dependent patients. Test–retest intraclass coefficients for a 0–10 days interval were in the range 0.65–0.79, whereas the Cronbach alpha coefficient indicated good internal consistency (range 0.7–0.89; Daeppen et al., 1998). The TOMHS-HWBS is very similar to the SF-36 but has rarely been used and to the best of our knowledge has not been validated. The EQ-5D is a standardized non-disease specific instrument for describing and assessing health-related QoL, in terms of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension comprises three levels, resulting in a total of 243 unique health states. It has demonstrated strong psychometric properties in general, but has a limited ability to discern small to moderate differences in health status (Janssen et al., 2008). Among 52 alcohol dependent patients, it showed

2.2. Analysis of currently used quality of life concepts in alcohol-dependent patients

We identified the life domains of these instruments by analyzing items concepts. For conceptual analysis, a concept was chosen for examination and then quantified. The focus was on examining the occurrence of selected terms within a text, although the terms could be implicit as well as explicit. While explicit terms were easy to identify, coding for implicit terms and deciding their level of implication was complicated by the need to base judgments on a somewhat subjective system. To limit the subjectivity, we also referred to validation articles and previous articles detailing these instruments. The identification of the domains within each instrument was double checked by two independent investigators (Amandine Luquiens and Henri-Jean Aubin); the second check was realized with a blind status regarding the list of domains established at first check. When the two investigators disagreed, a discussion led to a unified decision regarding the involved domain of life. Quality of life domain identification was made after reviewing all relevant scales. We have included as many domains as possible for accuracy, but some may overlap.

Please cite this article in press as: Luquiens, A., et al., Quality of life among alcohol-dependent patients: How satisfactory are the available instruments? A systematic review. Drug Alcohol Depend. (2012), <http://dx.doi.org/10.1016/j.drugalcdep.2012.08.012>

Table 1
Instruments designated as measuring quality of life in clinical trials among alcohol dependent patients.

	APQ	SF-36/SF-12	WHO- QOL-26	Q-LES-Q	EQ-5D	Koskenvuo QoL scale	VASQL	TOMHS HWBS
Litten et al. (2012)		×						
Gilbert et al. (2012)		×			×			
Fertig et al. (2012)		×						
Owens et al. (2011)					×			
Florez et al. (2010)				×				
Stedman et al. (2010)								
Moraes et al. (2010)		×						
Pettinati et al. (2009)		×						
LoCastro et al. (2009)		×	×					
Neto et al. (2008)	×							
Florez et al. (2008)					×			
Muhonen et al. (2008)							×	
Laaksonen et al. (2008)					×	×	×	
Sareen et al., 2007		×					×	
Johnson et al. (2004)				×				
Kiritze-Topor et al. (2004)		×						
Gual et al. (2003)		×						
Willenbring and Olson (1999)								×

only a trivial to medium responsiveness at 18 months (Gunther et al., 2008), and probably requires large patients samples to detect meaningful clinical differences. It has not been explicitly tested for measurement properties in individuals with alcohol use disorder (Gunther et al., 2007). The other scales refer explicitly to general QoL.

Among the scales, the Q-LES-Q measures the degree of enjoyment and satisfaction experienced by subjects in various areas of daily functioning. It is composed of 16 items each rated on a 5-point scale; a total score of items 1–14 is computed and expressed as a percentage of the maximal possible score of 70. There are two global items assessing medication and life satisfaction and contentment. The Q-LES-Q has primarily been used with anxiety and depressive disorder patients and presents good test–retest reliability and high internal consistency in a community sample ($n=67$): short-term (1–2 weeks) test–retest reliability of the 14 items score was 0.86, and for the overall rating of life satisfaction 0.71; internal consistency (Cronbach's alpha) was 0.90 (Rapaport et al., 2005).

The WHOQOL project was initiated in 1991 with the aim of developing an international, cross culturally comparable QoL assessment instrument. It assesses the individual's perceptions in the context of his/her culture and value systems in addition to his/her personal goals, standards and concerns. The WHOQOL instruments were developed collaboratively in a number of centers worldwide and have been widely field-tested. The WHOQOL-26 is an abbreviated version of the WHOQOL-100 questionnaire, and consists of 26 items, each rated on a 5-point Likert scale; from them, scores for four domains can be derived, namely "physical health", "mental health", "social relationship", and "environment". In addition, the WHOQOL-26 provides a score for overall quality of life, based on two items, with all scores range from 0 to 100. Internal consistency (Cronbach's alpha) coefficients of the WHOQOL-26 regarding a representative sample ($n=2073$) of the German population were 0.88 (physical health), 0.83 (mental health), 0.76 (social relationship), and 0.78 (environment; Angermeyer et al., 2000). In a sample of 103 individuals diagnosed with alcohol dependence, internal consistency of the WHOQOL-26 domains measured by Cronbach's alpha ranged from 0.73 to 0.79, indicating rather good reliability (Gunther et al., 2007). We found no psychometric information on the Koskenvuo QoL Scale and the VASQoL, either in the scientific or the gray literature.

We designate quality of life as any measure that is presented as such in the included studies. The scale used most frequently was the SF-36 ($n=9$), followed by the EQ-5D ($n=4$). Four instruments were used in only one trial each. In the last 3 years of the

search (i.e., 2010, 2011 and 2012), only the following three instruments were used: the SF-36 or SF-12, the Q-LES-Q and the EQ-5D. The methods and results of the 18 trials are presented in Table 2. Quality of life improved in only one trial (Johnson et al., 2004), using the Q-LES-Q as the primary outcome. The other trial in which QoL was the primary outcome did not show any significant difference between groups (Sareen et al., 2007). No other trials showed improvements in QoL with the other instruments: SF-36, SF-12, WHO-QOL-26, EQ-5D, APQ, Koskenvuo QoL Scale, VASQoL and the TOMHS-HWBS.

Interestingly, three trials found a difference between groups for the mental subscore of the SF36, including two positive trials for the primary outcome, suggesting that the physical subscore was either less impacted at the beginning or less sensitive to change. We note four positive trials for the primary outcome, which did not show a difference between groups in QoL; these trials used the APQ, the EQ-5D, the Koskenvuo QoL Scale, the VASQoL and the SF-36. Two trials showed an improvement with significant differences between groups for QoL using EQ-5D, which was not maintained over time (Florez et al., 2008, 2010).

3.2. Analysis of the current concept of quality of life in alcohol-dependent patients

The 27 domains investigated by the QoL instruments of the clinical trials are presented in Table 3. We categorized these domains into the following broader categories: relationships with others, activities, physical state, psychological state, financial concerns, medical care, legal problems and satisfaction with life. The instruments differed greatly from one another. In some of the trials, only one general question was asked (e.g., satisfaction with life in the VAS), whereas other trials explored a number of domains (up to 22 for the Q-LES-Q). Most of the instruments assessed social relationships (6/8); however, the EQ-5D and VASQoL did not. Family relationships were investigated in only four instruments: the APQ, the SF-36/12, the EQ-5D and the Q-LES-Q. Psychological well being was the most explored domain in 7 out of 8 trials. Interestingly, the domains related to a loss of physical autonomy (self-care, autonomy and mobility) were present in 6 of the 8 instruments; however, these domains are typically used to assess physical rather than psychological impairment.

4. Discussion

A total of 8 instruments were used in the 18 studies reviewed. Donovan et al. (2005) found 12 instruments in the review of studies

Table 2 (Continued)

Studies	Methods	Instruments	Results on quality of life: significant difference between groups	1st or 2ary outcome	Primary outcome: significant difference between groups (Yes/No)	Risk of bias assessment with Cochrane collaboration's tool
Stedman et al. (2010)	Design: randomized, double-blind placebo-controlled clinical trial Population: 362 male and female outpatients with a history of bipolar I disorder and alcohol dependence Intervention: add-on to lithium or divalproex; quetiapine (dose up to 400 mg/d over 7 days, followed by 300 to 800 mg/d) or placebo Length of study: 12 weeks Design: randomized controlled trial	Q-LES-Q	No	2	Change in proportion of heavy drinking days at 12 weeks; No	SB: unclear, no information PB: no bias DB: unclear, no information AB: mJTT RB: no bias
Moraes et al. (2010)	Population: 120 alcoholic patients aged between 20 and 60 years who had been enrolled for outpatient treatment Intervention: conventional outpatient treatment versus conventional treatment + home visits Length of study: 12 weeks Design: randomized controlled trial	SF-36	No except for mental subscore	2	Treatment adherence: Yes	SB: no bias PB: yes, no blinding DB: yes, no blinding AB: unclear, no information RB: yes, partial report
Pettinati et al. (2009)	Length of study: 12 weeks Design: randomized controlled trial Population: 624 alcohol-dependent patients Intervention: extended-release naltrexone (XR-NTX) 380 mg, XR-NTX 190 mg, or placebo Length of study: 24 weeks	SF-36	No except for mental subscore	2	Change in rate of heavy drinking days: Yes (380 mg)	SB: no bias, randomization procedure based on the biased coin principle PB: yes, personnel administering the injection was not blinded DB: no bias AB: no bias RB: no bias
LoCastro et al. (2009)	Design: randomized controlled trial Population: 1226 alcohol-dependent participants Intervention: naltrexone (100 mg/day) or placebo, acamprosate (3 g/day) or placebo, or both medications or placebo along with up to nine sessions of medical management; and moderate-intensity behavioral intervention (BI) versus no Length of study: 52 weeks	SF-12 and WHO-QOL-26	No except for physical subscore of SF12	2	Percentage of days abstinent, percentage of heavy drinking days and drinks per drinking day: No	SB: no bias, permuted block design, using blocks of 9, stratified by site PB: yes, no blinding to psychosocial treatment DB: yes, research assistants were not blinded to psychosocial treatment AB: no bias RB: no bias

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Table 2 (Continued)

Studies	Methods	Instruments	Results on quality of life: significant difference between groups	1st or 2ary outcome	Primary outcome: significant difference between groups (Yes/No)	Risk of bias assessment with Cochrane collaboration's tool
Neto et al. (2008)	Design: open label randomized controlled trial Population: 209 alcohol-dependent patients Intervention: sequential combined treatment and treatment as usual Length of study: 180 days Design: naturalistic, randomized and open-label trial	APQ	No	2	Time to first relapse: Yes	SB: no bias PB: yes, no blinding DB: yes, no blinding AB: no bias RB: no bias
Florez et al. (2008)	Population: 102 alcohol-dependent patients Intervention: topiramate versus naltrexone Length of study: 6 months Design: randomized clinical trial	EQ-5D	Yes at 3 months. No at 6 months	2	Composite outcome measure: No	SB: unclear, no information PB: yes, no blinding DB: yes, no blinding AB: no bias RB: no bias
Muhonen et al. (2008)	Population: 80 alcohol-dependent outpatients with major depressive disorder Intervention: memantine 20 mg/day or escitalopram 20 mg/day Length of study: 26 weeks Design: randomized, open-label trial, multicentre naturalistic study in two phases	VASQL	No	2	Change in MADRS and HAMA: No	SB: no bias, random permuted blocks PB: no bias DB: unclear, no information AB: yes, attrition bias due to handling of incomplete data RB: no bias
Laaksonen et al. (2008)	Population: 243 voluntary treatment-seeking alcohol-dependent adult outpatients Intervention: supervised Naltrexone, Acamprosate or Disulfiram, 50, 1998, or 200 mg, respectively, per day, plus a brief manual-based cognitive-behavioral intervention Length of study: 119 weeks (2.5 years) Design: randomized controlled trial	EQ-5D, Koskenvuo QoL scale and VASQL	No	2	Time (days) to first heavy drinking day, and time during the first 3 months to the first drinking day after medication started: Yes during continuous medication period (1–12 weeks), no after	SB: no bias, random permuted blocks PB: yes, no blinding DB: yes, no blinding AB: no bias RB: no bias
Sareen et al. (2007)	Population: 60 patients with chronic pancreatitis Intervention: the control group continued their usual care as directed by their physicians. Patients in the yoga group, in addition, received biweekly yoga sessions Length of study: 12 weeks	SF36	No	1	SF36: No	SB: no bias PB: yes, no blinding DB: yes, no blinding (self assessment) AB: yes, attrition bias due to handling of incomplete outcome data; dropouts were eliminated from all analyses RB: no bias

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Table 2 (Continued)

Studies	Methods	Instruments	Results on quality of life: significant difference between groups	1st or 2ary outcome	Primary outcome: significant difference between groups (Yes/No)	Risk of bias assessment with Cochrane collaboration's tool
Johnson et al. (2004)	Design: double-blind, randomized, controlled trial Population: 150 alcohol-dependent individuals Intervention: topiramate vs placebo. Length of study: 12 weeks	Q-LES-Q	Yes	1	Q-LES-Q: Yes	SB: unclear, no information PB: no bias DB: unclear, no information AB: attrition bias due to handling of incomplete outcome data RB: no bias
Kiritze-Topor et al. (2004)	Design: open-label randomized trial Population: 422 patients Intervention: standard care alone or standard care with acamprosate	SF-36	No (yes for all dimensions except for general health)	2	Change from baseline on the Alcohol-Related Problems Questionnaire: Yes	SB: no bias PB: yes, no blinding DB: yes, no blinding AB: no bias (censoring method) RB: no bias
Gual et al. (2003)	Length of study: 1 year Design: double-blind, placebo-controlled randomized trial Population: 83 alcohol-dependent patients with current depressive symptoms Intervention: sertraline (50–150 mg/day) or placebo Length of study: 24 weeks Design: randomized controlled trial	SF-12	No except for mental health subscore	2	Rate of relapse into alcohol consumption and rate of response on the Montgomery and Asberg Depression Rating Scale: No	SB: no bias PB: no bias DB: no bias AB: no bias RB: no bias
Willenbring and Olson (1999)	Population: 105 male veterans with severe medical complications caused by alcoholism and recent drinking Intervention: integrated outpatient treatment referral to standard alcoholism and medical treatment Length of study: 2 years	TOMHS HWBS	No	No definition of a primary outcome	No definition of a primary outcome	SB: no bias PB: yes, no blinding DB: yes, no blinding AB: yes, attrition bias due to handling of incomplete outcome data RB: no bias

NA: not applicable; SB: selection bias; PB: performance bias; DB: detection bias; AB: attrition bias; RB: reporting bias; mITT: modified intention to treat.

Table 3
Domains investigated by quality of life instruments used in clinical trial among alcohol dependent patients.

Categories	Domains	APQ	SF-36/SF-12	WHO QoL26	Q-LES-Q	EQ-5D	Koskenvuo QoLscale	VAS	TOMHS HWBS
Relation to others	Family relationships	x	x		x	x			
	Problems with children	x							
	Social relations	x	x	x	x		x		x
Activities	Work	x	x	x	x	x			
	Leisure	x		x	x	x			
	Social responsibilities/daily activities	x	x	x	x	x			x
Physical state	Autonomy	x	x		x	x			x
	Self-care	x	x		x	x			
	Mobility	x	x	x	x	x			
	Physical activity	x	x	x	x	x			x
	Sexual activity	x	x	x	x	x			
	Health state	x	x	x	x	x			x
	Physical appearance	x	x	x	x	x			
Psychological state	Psychological well-being	x	x	x	x	x	x		x
	Security								
	Energy		x						
	Cognitive functioning								
	Self esteem								
	Weight/appetite	x							
	Sleep								
	Values/spirituality								x
	Living conditions								
	Budget	x							
	Medical care/hospitalization	x							
	Legal problems								
	Satisfaction with life	x							x

that explored QoL in alcohol-dependent patients in epidemiological studies; however, our study focused on randomized controlled clinical trials to report the strongest evidence. Randomized controlled clinical trials are generally more rigorously designed and have the advantage of offering an intervention, which allows the instruments' sensitivity to change to be evaluated. We have focused on the domains explored by the instruments for QoL, which has never been done for alcohol-dependent patients.

The following 17 instruments found by Donovan et al. (2005) were not present in our review: the Centers for Disease Control and Prevention's quality of life measures, the SF-20, the Quality of Life Index, a Brief Quality of Life Inventory, the Treatment Outcome Profile, the Schedule of Evaluation of Individual Quality of Life, the Cantril's Self-Anchoring Ladder of Life Satisfaction, Quality of Life Inventory, the Rotterdam Symptoms Checklist, the Quality of Well-Being Scale, the Chubon's Life Situation Survey, the Multidimensional Index of Quality of Life, the Satisfaction With Life Scale, the General Health Questionnaire, the Life Situation Survey, the Treatment Outcome Profile and the Munich List of Life Dimensions. Most of those instruments were developed for general or other chronic conditions. If the use of generic instruments was initially needed to emphasize the legitimacy of assessing QoL within the alcohol-dependence field, their contribution is now restricted to capture the changes that are specific to alcohol dependence. In 2009, Zubaran mentioned the ALQoL-9 (Malet et al., 2006) in his review, which has been validated in a population of alcohol-dependent patients but directly derived by item restriction from the SF-36, a generic instrument. If we add our findings to those published by Donovan et al. (2005), at least 25 instruments have been used to measure the QoL in alcohol-dependent patients. We showed that the eight instruments used in the clinical trials had a high level of heterogeneity. Therefore, it would be worthwhile to standardize the QoL measure in this

population to enable comparisons between studies and systematic reviews.

No specific instrument has ever been developed to assess the change in QoL among alcohol-dependent patients. However, in other chronic conditions, clinicians and researchers have specific instruments to measure QoL (e.g., cancer (Macquart-Moulin et al., 1997) and cardiovascular disease (Stamler et al., 1987)). We have shown that only one trial was able to demonstrate a significant difference between the intervention and control groups in the QoL outcome, and that trial had QoL as a primary outcome. We see three possible explanations for the other negative results. First, QoL may not significantly change after treatment in alcohol-dependent patients, which would mean that QoL is not a solid concept or that treatments are not effective in improving QoL. Second, QoL in patients with alcohol dependence may be altered in a specific way and must be measured with a specific instrument. In other words, the results could be negative due to a lack of specificity of the instruments in measuring the relevant domains for these patients. Third, the study design may not be suitable for measuring QoL because QoL is usually a secondary endpoint. Therefore, negative results could be due to an inadequate design. The risk of an indiscriminate measurement of Patient Reported Outcomes (PROs) is producing ineffective and confounding data (Arpinelli and Bamfi, 2006). Results would be optimized in studies measuring QoL as a primary outcome with an appropriate sample size and with adequate time of measurement. Certainly, these hypotheses are not mutually exclusive. The Food and Drug Administration (FDA) encourages specific PRO instruments to support labeling of medical products (FDA, 2009). The development of a rigorous patient-reported-outcome QoL instrument that is specific to patients with alcohol use disorders and that is patient-focused would allow clinicians to have an effective instrument to administer to their patients (Arpinelli and Bamfi, 2006).

Please cite this article in press as: Luquiens, A., et al., Quality of life among alcohol-dependent patients: How satisfactory are the available instruments? A systematic review. Drug Alcohol Depend. (2012), <http://dx.doi.org/10.1016/j.drugalcdep.2012.08.012>

In addition, we have demonstrated some confusion of concepts: to measure QoL, some authors use scales of general health or problems related to substance use. The scales of general health status, such as the SF-36/12 and the EQ-5D, place an emphasis on physical state. Moreover, Miller noted in 2009 that “the dominance of a health approach for addiction treatment may not be reflective of an addict’s main concerns” (Miller and Miller, 2009). The measures of alcohol-related problems have queried broader domains, including societal facets. However, if the measures of alcohol-related problems have the advantage of adhering to the current definition of addiction, these measures cannot be superimposed by the concept of QoL. These scales do not explore a perceived state of the patient that corresponding to his/her QoL, rather, the scales explore the occurrence of negative events, but not how important these events are to patients. However, it appears that two patients can attribute a completely different importance to a similar negative event linked to alcohol consumption.

Furthermore, if many surveyed domains are common, the question wording and therefore the answers can differ widely. For example, the budget formulation items vary widely depending on the perspective. The Q-LES-Q asks, “How satisfied have you been with your economic status?” while the APQ asks, “Have you had any debts?” The same situation can lead to different answers depending on whether one examines QoL directly and the dependence severity or alcohol-related problems. QoL measurements have been conceived to reflect the impact of diseases and interventions in daily life from the patient’s perspective (Lep lege, 1999). This sliding of concept from QoL to alcohol-related problems could be the consequence of an initial misunderstanding in the construction of QoL instruments; the instruments are meant to reflect a perceived health or a well-being state, which is not similar to a subjective response to items that are meant to reflect health or a well-being state in experts’ minds. The self-administration of these scales only implicates subjective answers; answers to questions that are for most of them asked by experts.

A PRO insures the subjectivity of the outcome, but not its clinical pertinence. A pertinent PRO should be patient-focused. One way to achieve this need could be to build the instrument from the patients themselves, via qualitative analysis of interviews with alcohol-dependent patients. This methodology could allow identification of the most impacted domains of life in this particular population and those aspects that are most sensitive to change, thereby promising real usefulness in assessing the efficacy of interventions among alcohol-dependent patients.

5. Conclusion

It is undeniable that improvement in QoL is a daily concern for alcohol-dependent patients and the ultimate treatment goal for many of them. The lack of access to care by some individuals suffering from alcohol use disorders led us to investigate QoL as an attempt to better meet their needs. The instruments currently used to assess QoL may not collect information that is both relevant and accurate to the lives of these patients. Quality of life is often criticized for its elusive nature. This issue should be further discussed in scientific arguments. We should avoid considering QoL equivalent to other concepts, such as health status or severity of problems related to alcohol use. We hope that this review will provide clinicians with a broad and precise view of the existing instruments so that clinicians may wisely choose the one that best fits the desired outcome measure. The development of an original PRO instrument specifically for alcohol-dependent patients, responding to a rigorous patients-focused methodology, would overcome the scattering of data regarding the QoL in alcohol-dependent patients.

Role of funding source

None.

Contributors

Dr Aubin reviewed and commented the protocol and the manuscript. Dr Reynaud reviewed the article. Dr Luquiens has written the protocol, processed to the review, analyzed the data and written the manuscript. Pr Falissard reviewed and commented the manuscript and gave a methodological expertise.

Conflict of interest

Dr Aubin has received sponsorship to attend scientific meetings, speaker honoraria and consultancy fees from Pfizer, McNeil, GlaxoSmithKline, Sanofi-Aventis, Lundbeck, D&A Pharma and Merck-Sereno. Dr Reynaud has received in the last 3 years sponsorship to attend scientific meetings, speaker honoraria, funding, and consultancy fees from Merck-Sereno, Shering Plough, Lundbeck and Bristol-Myers-Squibb. Dr Luquiens has no conflict of interest. Pr Falissard has no conflict of interest.

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Données récentes sur la qualité de vie en alcoologie (François et al. 2015)

L'article « François, C., N. Rahhali, et al. (2015). "The Effects of as-Needed Nalmefene on Patient-Reported Outcomes and Quality of Life in Relation to a Reduction in Alcohol Consumption in Alcohol-Dependent Patients." PLoS One 10(6): e0129289.» publié en anglais est ici synthétisé en français, puis inséré dans sa version complète en anglais.

Introduction et méthodes

Depuis la revue de la littérature réalisée en 2012 et avant le développement d'un instrument de type PRO spécifique au trouble d'usage d'alcool, ont eu lieu plusieurs essais cliniques dans l'alcoolodépendance testant l'efficacité du nalméfène à visée de réduction de consommation d'alcool. ESENSE 1 et ESENSE 2 sont deux essais randomisés contrôlés contre placebo, en double aveugle, jumelés, d'une durée de six mois, testant l'efficacité du nalméfène 18 mg administré à la demande, chez des patients alcoolodépendant, pendant six mois (Gual, He et al. 2013; Mann, Bladström et al. 2013). Les patients bénéficiaient en plus d'un accompagnement psychosocial. Les critères principaux de jugement de ces essais étaient l'évolution de la consommation totale d'alcool en g/jour et le nombre de jour de consommation excessive entre les 4 semaines précédant la sélection des patients et le sixième mois de traitement. Les résultats poolés de ces deux études dans le sous-groupe des patients restant à haut risque de consommation selon l'OMS au cours des 4 semaines précédant la randomisation ont permis de montrer une supériorité du nalméfène sur le placebo pour ces critères (van den Brink, Aubin et al. 2013).

La présente étude est une analyse post hoc des résultats en termes de qualité de vie et de conséquences négatives liées aux consommations d'alcool, dans ce même sous-groupe de patients. Le but de cette analyse était d'étudier l'effet du nalméfène sur la qualité de vie et les

conséquences négatives liées à l'alcool chez ces patients à six mois, et d'étudier la relation entre ces critères et le comportement de consommation d'alcool.

Les trois mesures rapportées ici étaient la SF-36, L'EQ-5D et la DrInC. Il a été choisi d'associer deux mesures de qualité de vie liées à la santé en tenant compte des limites soulignées par la précédente revue de la littérature de chacune de mesures dans cette population. La DrInC (Miller and Longabaugh 1995) est une échelle auto-administrée de 50 items, développée pour évaluer la survenue de conséquences négatives des consommations d'alcool, sur 5 domaines: physique, interpersonnel, social, et contrôle des impulsions. La période de rappel est de 3 mois, et le score va de 0 à 135 (niveau le plus élevé de conséquences).

Il a été utilisé un modèle mixte pour mesures répétées pour comparer l'évolution de ces trois variables à 12 et 24 semaines, la valeur à l'inclusion a été incluse comme co-variable, et le pays, le sexe, le temps et l'effet traitement comme effets fixes. La corrélation entre ces trois variables et les changements de consommation d'alcool ont été testées par le test de Pearson.

Résultats

1322 patients ont été randomisés et les 667 patients toujours un niveau de risque élevé lors des 4 semaines précédant la randomisation (population cible) ont été gardés pour les analyses.

Dans cette population, le nalméfène a significativement amélioré le sous-score mental, le sous-score physique de la SF-36, l'index d'utilité de l'EQ-5D ainsi que le score d'état de santé de l'EQ-5D, à 12 et 24 semaines. L'amélioration du sous score mental de la SF-36 à 24 semaines était significativement et modérément corrélé à la réduction du nombre de consommation excessive et à la consommation totale d'alcool ($r=-0.2$ et -0.2). Toutes les dimensions de la SF-36 étaient significativement plus améliorées dans el groupe nalméfène sauf le "rôle physique". L'amélioration du score d'état de santé de l'EQ-5D à 24 semaines

était significativement et modérément corrélé à la réduction du nombre de consommation excessive et à la consommation totale d'alcool ($r=-0.2$). La différence entre les 2 groupes et le placebo pour le score DrInC n'était significatif qu'à 24 semaines (période de rappel de 3 mois). A 24 semaines, l'amélioration du score DrInC était corrélé significativement et modérément à la diminution du nombre de jours de consommation excessive et de la consommation totale d'alcool ($r=0.2$).

Discussion

Cette étude a pu montrer que la réduction de la consommation d'alcool sous nalméfène était associée à des améliorations de la qualité de vie liée à la santé et d'une réduction des conséquences négatives liées à la consommation. Le caractère modéré de cette corrélation montre bien qu'il reste nécessaire de documenter par des PRO l'évolution des patients lors d'essais cliniques testant l'efficacité de médicaments.

La taille des améliorations décrites sur la SF-36 et l'EQ-5D ont pu montrer une pertinence clinique en se référant aux index disponibles pour ces échelles.

Les limites principales de cette analyse sont son caractère post-hoc et la population d'analyse concernant le sous-groupe de patients continuant à avoir une consommation à risque entre l'inclusion et la randomisation. L'absence d'instrument de type PRO mesurant la QVLS spécifique au trouble d'usage d'alcool, au moment de la planification de l'étude, a contraint les auteurs à utiliser deux instruments, la SF-36 et l'EQ-5D, ayant des limites dans cette population, notamment une faible sensibilité au changement en ce qui concerne l'EQ5D, et certains sous-scores de la SF-36, une partie de l'information relative à la qualité de vie pourrait donc manquer du fait de ces limites et du manque de spécificité des instruments utilisés.

RESEARCH ARTICLE


The Effects of as-Needed Nalmefene on Patient-Reported Outcomes and Quality of Life in Relation to a Reduction in Alcohol Consumption in Alcohol-Dependent Patients

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Citation: François C, Rahhali N, Chalem Y, Sørensen P, Luquiens A, Aubin H-J (2015) The Effects of as-Needed Nalmefene on Patient-Reported Outcomes and Quality of Life in Relation to a Reduction in Alcohol Consumption in Alcohol-Dependent Patients. PLoS ONE 10(6): e0129289. doi:10.1371/journal.pone.0129289

Academic Editor: Osama Ali Abulseoud, Mayo Clinic, UNITED STATES

Received: January 28, 2015

Accepted: May 6, 2015

Published: June 8, 2015

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Data Availability Statement: All relevant data are within the paper.

Funding: The authors thank Steve Clissold and David Figgitt, Content Ed Net, for providing valuable editorial support in the preparation of the article. The study was funded by Lundbeck and funding for editorial support was provided by Lundbeck SAS, France. Lundbeck provided support in the form of salaries for authors CF, NR, YC and PS. The funding source was involved in the design of the study, data collection and analysis, decision to publish, and

Abstract

Background

The objective of this article was to investigate the effect of as-needed nalmefene on health-related quality of life (HRQoL) in patients with alcohol dependence, and to relate changes in drinking behavior and status to HRQoL outcomes.

Methods

This *post hoc* analysis was conducted on a pooled subgroup of patients with at least a high drinking risk level (men: >60 g/day; women: >40 g/day) who participated in one of two randomized controlled 6-month studies, ESENSE 1 and ESENSE 2. Patients received nalmefene 18 mg or placebo on an as-needed basis, in addition to a motivational and adherence-enhancing intervention (BRENDA). At baseline and after 12 and 24 weeks questionnaires for the Medical Outcomes Study (MOS) 36-item Short-Form Health Survey (SF-36), European Quality of life-5 Dimensions (EQ-5D) and the DrInC-2R were completed.

Results

The pooled population consisted of 667 patients (nalmefene: 335; placebo: 332), with no notable between-group differences in baseline patient demographics/characteristics. At week 24, nalmefene had a superior effect compared to placebo in improving SF-36 mental component summary scores (mean difference [95% CI], p-value: 3.09 [1.29, 4.89]; p=0.0008), SF-36 physical component summary scores (1.23 [0.15, 2.31]; p=0.026), EQ-5D utility index scores (0.03 [0.00, 0.06]; p=0.045), EQ-5D health state scores (3.46 [0.75, 6.17]; p=0.012), and DrInC-2R scores (-3.22 [-6.12, 0.33]; p=0.029). The improvements in SF-36 mental component summary scores at week 24, and the DrInC-2R total score

preparation of the manuscript. The specific roles of the authors are listed in the authors contributions section.

Competing Interests: The authors have the following interests. The authors thank Steve Clissold and David Figgitt, Content Ed Net, for providing valuable editorial support in the preparation of the article. The study was funded by Lundbeck and funding for editorial support was provided by Lundbeck SAS, France. Lundbeck has European marketing approval for Selincro (nalmefene). Henri-Jean Aubin has received honoraria and travel grants from Lundbeck, Merck Serono, Ethypharm, D&A Pharma, Pfizer, and Bioprojet. Amandine Luquiens has received honoraria and travel grants from Lundbeck. Clément François, Nora Rahhali, Ylana Chalem, and Per Sørensen are employees of Lundbeck. There are no further patents, products in development or marketed products to declare. This does not alter their adherence to all the PLOS ONE policies on sharing data and materials, as detailed online in the guide for authors.

change from baseline to week 24, were significantly correlated to reductions in heavy drinking days and total alcohol consumption at week 24.

Conclusions

As-needed nalmefene significantly improved almost all patient-reported HRQoL measures included in SF-36 and EQ-5D compared with placebo. These HRQoL gains were significantly correlated to reduced drinking behavior, as determined by reductions in heavy drinking days and total alcohol consumption.

Introduction

Alcohol dependence has been estimated to affect 8 million persons in the USA [1] and 14.6 million in Europe [2] and, as such, is a major public health concern. It places enormous pressure on families, healthcare systems and society which increases with increasing alcohol consumption [3–5]. Alcohol is one of the most important avoidable risk factors for global burden of disease and disability. For example, in 2004, 3.8% of all global deaths (6.3% for men and 1.1% for women) and 4.6% of disease burden and injury (7.6% for men and 1.4% for women) were attributed to alcohol [6]. These rates are similar to those associated with the use of tobacco [6].

The traditional goal for the management of alcohol dependence has been abstinence, and this has been the primary endpoint in many clinical trials. However, less than 10% of patients with alcohol use disorders are undergoing treatment and the unwillingness to engage in an abstinence programme is a major roadblock to therapeutic success [7]. The availability of treatments aimed at reducing alcohol intake is likely to increase the proportion of patients entering treatment programmes and is increasingly being accepted as a viable therapeutic strategy [7–12].

Patients with alcohol dependence have lower levels of quality of life (QoL) compared with general population norms and compared with other chronic health conditions such as diabetes and heart failure [13–15]. Additionally, frequent or episodic heavy drinking patterns in non-dependent individuals are associated with reduced QoL compared with the general population. Importantly, regarding the clinical management of alcohol-dependent individuals, it has been shown that marked reductions in drinking, without complete abstinence, are associated with significant improvement in QoL [13–16].

A number of studies have evaluated health-related QoL (HRQoL) as the primary outcome measure in treatment trials of alcohol-dependent patients, generally with abstinence as the treatment goal [15–21]. In particular, the Medical Outcomes Study (MOS) 36-item Short-form Health Survey (SF-36) and the European Quality of life-5 Dimensions (EQ-5D) instruments have been used widely in clinical trials in many disease settings, including alcohol use disorders [22]. Acamprosate plus social support produced a general improvement in all SF-36 dimensions and summary scores after 3 months, with a further slight improvement after 6 months in a study involving alcohol-dependent patients [18]. Another study evaluated changes in HRQoL in alcohol-dependent patients entering a 3-week inpatient treatment program and found that scores for the eight individual SF-36 dimensions, as well as the mental and physical summary scores, had improved significantly by the end of treatment compared with baseline [15]. Frischknecht and colleagues reported that improved drinking behavior was associated with a better HRQoL after 7-years' post-treatment follow-up in alcohol-dependent patients who underwent an initial 6-week inpatient and 1-month outpatient treatment program aimed at abstinence [16]. In a recent study in adults with alcohol dependence, a combination of

medical treatment (naltrexone, acamprosate or disulfiram) with cognitive behavioral therapy was shown to reduce symptoms of depression and improve patients' HRQoL as measured with EQ-5D. In particular, at 12, 52 and 119 weeks, treatment was associated with significant improvements from baseline for the dimensions of sleep, action, pain, and mood EQ-5D [21].

Nalmefene is an opioid system modulator with antagonistic activity at the μ and δ receptors, and partial agonist activity at the κ -receptor [23]. It appears to restore the balance of a dysregulated motivational system by reducing the reinforcing effect of alcohol, and thereby reducing the urge to drink alcohol. Treatment with nalmefene on an as-needed basis reduces total alcohol consumption and the number of heavy drinking days compared with placebo, as was shown in the two controlled 6-month efficacy studies, ESENSE 1 and ESENSE 2 [24,25]. Pooled data from ESENSE 1 and 2 involving alcohol-dependent patients with at least a high drinking risk level (as defined by the World Health Organization (WHO) [3]), demonstrated that nalmefene was associated with a superior effect compared with placebo in reducing the number of heavy drinking days and total alcohol consumption at month 6 [26]. Nalmefene was recently granted market approval in the European Union for the reduction of alcohol consumption in adult patients with alcohol-dependence who have at least a high drinking risk level according to the WHO (>60 g/day for men and >40 g/day for women [3]) and who continue to have a high drinking risk level 2 weeks after initial assessment [27].

This article presents a *post hoc* analysis of the high drinking risk alcohol-dependent subgroup from ESENSE 1 and 2. This sub-group was selected since a large improvement in drinking behavior was observed in both trials for the up to 2 weeks during the period between screening and randomization [24,25]. This phenomenon has been reported previously and means that a substantial fraction of the patients would be treated without a prospect of further improvement [26]. The primary aim of this analysis was to investigate the effect of as-needed nalmefene on HRQoL and a measure of the adverse consequences of alcohol abuse as assessed by patient-reported outcomes, and to relate changes in drinking behavior and status to HRQoL outcomes.

Methods

Full details of the methods employed in ESENSE 1 and 2 have been published previously [24–26] and below is an overview to provide context for the reader.

Study Design and Population

This analysis is based on two 6-month randomized, double-blind, placebo-controlled, efficacy studies, ESENSE 1 and ESENSE 2, which assessed nalmefene on an as-needed basis in a subgroup of patients with at least a high drinking level risk. The two studies were identical in design [24,25]. All patients took part in a motivational intervention programme (BRENDA) to support behavioral change and to enhance adherence to treatment [28].

Men and women aged ≥ 18 years with a primary diagnosis of alcohol dependence according to the Diagnostic and Statistical Manual of Mental Disorders [29], assessed with the Mini-International Neuropsychiatric Interview [30] were evaluated for eligibility at an initial screening visit. Both studies were conducted in accordance with the Declaration of Helsinki and the ICH Harmonized Tripartite Guideline for Good Clinical Practice, and were approved by the ethics committees at each study site. All patients provided written informed consent.

Study Procedures and Assessments

One to two weeks after screening, patients were randomized 1:1 to 24 weeks double-blind as-needed treatment with nalmefene 18 mg or placebo. Patients were instructed to take one tablet

each day they perceived a risk of drinking alcohol (as-needed dosing), preferably 1–2 h prior to anticipated time of drinking, but otherwise as soon as drinking had started. No specific treatment goal was defined, i.e. both abstinence and a reduction in alcohol consumption were acceptable. Assessments of efficacy and safety have been published elsewhere [24–26]. The focus of this analysis was to relate changes in drinking behavior and status with a measure of alcohol-associated problems (Drinker Inventory of Consequences [DrInC-2R]) and to measures of HRQoL as assessed by patient-reported outcomes using two relevant instruments: the SF-36 and the EQ-5D questionnaires which were administered at baseline, week 12 and week 24.

SF-36. The SF-36 is a patient-reported outcome instrument that was developed as a generic measure of perceived health status [31]. The standard SF-36 is a self-rated questionnaire comprising 36 questions which generate 8-domain health profiles using 3- to 5-point Likert scales. These are: physical functioning, bodily pain, role limitations due to physical problems, general health perception, mental health, energy and vitality, role limitations due to emotional problems, and social functioning. The first four domains are aggregated to create the Physical Component Summary (PCS) and the second four domains combined to create the Mental Component Summary (MCS).

Scores for each domain are calculated by using scoring algorithms detailed in the user's manual by summing the item responses in each domain and then into a 0–100 range for each of the eight domains [32]. These are then standardized using means and standard deviations for the general population. Higher scores correspond to better health status or well-being. Systematic comparisons of the SF-36 with other commonly-used HRQoL instruments indicate that the SF-36 includes eight of the most frequently measured health domains, indicating content validity and relevance as a generic HRQoL measure [13,33]. The SF-36 is the most extensively used instrument for determining generic patient-reported outcome measures in general and specific populations, including individuals with alcohol use disorders [13]. It has proven useful for comparing the burden of different diseases, differentiating the health benefits of different treatments and for screening individual patients. Studies have demonstrated the reliability and validity of the SF-36 in alcohol-dependent populations [18].

EQ-5D. The EQ-5D is a generic measure of HRQoL in which health status is defined in terms of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression [34,35]. Each dimension has three qualifying levels of response roughly corresponding to 'no problems', 'some difficulties/problems', and 'extreme difficulties'. EQ-5D defines a total of 243 theoretically possible unique health states. The 5 items allow the calculation of a utility index ranging between -0.594 (the worst) and 1 (the best) [35]. For the rating of own health state status on the vertical visual analogue scale, a higher scores means a better health state [36].

DrInC. The Drinker Inventory of Consequences (DrInC) is a self-administered questionnaire comprising 50 items [37]. It was designed to measure adverse consequences of alcohol abuse in five areas: physical, intrapersonal, social, interpersonal and impulse control. The scale provides a previous 3-month measure of adverse consequences, and scores range from 0 to 135. The higher the total DrInC score the greater the adverse consequences for the patient.

Statistical Analyses

For the current subgroup analyses the target efficacy population comprised all randomized patients who had at least one valid post-baseline assessment of both co-primary efficacy variables (heavy drinking days and total alcohol consumption) and at least a high drinking risk level (men: alcohol consumption >60 g/day; women: alcohol consumption >40 g/day), as defined by the WHO [3] at both screening and randomization. The baseline for drinking variables was

Table 1. Baseline characteristics/demographics, including patient-reported outcomes, in patients with a high drinking risk level (target efficacy population) [adapted from [27]].

	High drinking risk level at screening and randomization (target population)		
	Placebo (n = 332)	Nalmefene (n = 335)	TOTAL (n = 667)
Race, Caucasian	329 (99.1%)	333 (99.4%)	662(99.3%)
Sex, Male	216 (65.1%)	223 (66.6%)	439(65.8%)
Age (years)	48.7 (10.5)	48.4 (10.5)	48.5 ± 10.5
Body Mass Index (kg/m ²)	26.1 (4.4)	26.0 (4.8)	26.0 ± 4.6
Age at onset of problem drinking (years)	35.1 (11.6)	35.6 (12.3)	35.3 ± 11.9
Total monthly heavy drinking days (days)	22.4 (6.0)	22.9 (5.9)	22.6 ± 5.9
Total alcohol consumption (g/day)	103.3 (44.5)	107.7 (45.5)	105.5 ± 45.0
Clinical Global Impression—Severity of Illness	4.3 (1.4)	4.3 (1.4)	4.3 ± 1.4
Drinker inventory of consequences (DrInC) total score	42.2 (22.2)	41.1 (22.3)	41.6 ± 22.2
Alcohol dependence scale total score	13.3 (5.7)	14.0 (6.0)	13.7 ± 5.8
Current smoker	192 (57.8%)	184 (54.9%)	376(56%)
Living alone	99 (29.8%)	88 (26.3%)	187(28%)
Previously treated for alcohol dependence	112 (33.7%)	105 (31.3%)	217(32.5%)
Previously treated for alcohol withdrawal symptoms	59 (17.8%)	49 (14.6%)	108(16.2%)
Family history of alcohol problems	209 (63.0%)	211 (63.0%)	420(63.0%)

Data are mean (SD) or number of patients (%).
SD, standard deviation.

doi:10.1371/journal.pone.0129289.t001

defined as the month preceding the screening visit. For all other variables, the baseline was defined as the assessment at the screening visit.

Analysis of the pooled subgroup of patients with at least a high drinking risk level assessed changes from baseline in patient-reported outcomes using a mixed model repeated measures analysis (MMRM). The MMRM model used observed data and included the baseline value as a covariate and country, sex, time in weeks (Weeks 12 and 24), and treatment as fixed effects. The baseline value-by-time interaction and treatment-by-time interaction were also included in the model, and an unstructured covariance matrix was used.

Pearson correlation coefficients were estimated for changes in alcohol consumption (number of heavy drinking days and total alcohol consumption, from van den Brink and colleagues [26]) vs. changes in patient-reported outcomes in both the nalmefene and placebo groups and they were adjusted for baseline values of patient-reported outcomes.

All statistical tests were two-sided and p values < 0.05 were considered to be statistically significant. The statistical software used was SAS, Version 9.2.

Results

1322 patients were randomized to treatment and of these 667 patients (50.5%) had at least a high drinking risk level at both screening and randomization (target population): 335 patients in the nalmefene group and 332 patients in the placebo group. Details of the target population included in this analysis have been published previously and there were no notable differences between the nalmefene and the placebo groups (Table 1) [26]. The mean age at baseline was 48 years, two-thirds of the patients were males, the cohort was almost exclusively Caucasian (99%) and the mean age at the onset of problem drinking (defined as drinking that starts to adversely affect an individual's personal or professional life, or when the individual loses control over their drinking) was 35 years. Mean BMI at baseline was 26 kg/m², and one-third of

patients had previously been treated for alcohol dependence and 16% for alcohol withdrawal symptoms (Table 1). Mean (\pm standard deviation) baseline HRQoL scores on the SF-36 and EQ-5 dimensions surveys, and DrInC questionnaire scores were virtually identical in the nalmefene and placebo groups: SF-36 MCS score (40.9 ± 12.6 vs. 40.9 ± 12.6), SF-36 PCS score (50.2 ± 8.0 vs. 50.8 ± 8.0), EQ-5D utility index score (0.78 ± 0.21 vs. 0.80 ± 0.21), EQ-5D health state score (67.9 ± 17.2 vs. 68.9 ± 17.7), and DrInC total score (41.5 ± 22.0 vs. 41.3 ± 22.1), respectively.

Patient-Reported Outcomes

Using a MMRM analysis in the target efficacy population, nalmefene was shown to significantly improve SF-36 MCS, SF-36 PCS, EQ-5D utility index score and EQ-5D health state score after 12 and 24 weeks of treatment (Table 2). The changes from baseline in SF-36 MCS and SF-36 PCS were significantly greater for nalmefene versus placebo by week 12 and were further improved by week 24 as shown in Figs 1 and 2. The improvement in SF-36 MCS at week 24 was correlated to reductions in heavy drinking days ($r = -0.1941$; $p < 0.0001$) and total alcohol consumption ($r = -0.2061$; $p < 0.0001$) (Table 3).

In the nalmefene group, SF-36 scores for all dimensions with the exception of 'role physical' were significantly improved from baseline to week 24 compared with placebo (Table 4). 'Role physical' exhibited a trend towards improvement (mean \pm standard deviation difference vs. placebo 1.36 ± 0.71 , $p = 0.0561$).

EQ-5D utility index scores were improved to a significantly greater extent by nalmefene compared with placebo after 12 ($p = 0.0185$) and 24 ($p = 0.0455$) weeks (Table 2). Likewise, EQ-5D health state scores were also improved to a significantly greater extent by nalmefene compared with placebo after 12 ($p = 0.0191$) and 24 ($p = 0.0124$) weeks (Table 2). There was a significant correlation between improvement in EQ-5D health state scores and a reduction in the number of heavy drinking days ($r = -0.2023$; $p < 0.0001$) and also with a reduction in total

Table 2. Adjusted Mean changes in SF-36, EQ-5D and DrInC scores from baseline to week 12 and week 24 in patients with a high drinking risk level (MMRM, target efficacy population).

		Change from baseline to Week 12		Difference to Placebo baseline to Week 12			Change from baseline to Week 24		Difference to Placebo baseline to Week 24		
		N	Mean \pm SE	Mean \pm SE	95% CI	p-value	N	Mean \pm SE	Mean \pm SE	95% CI	p-value
SF-36 MCS score	PLA	268	2.10 \pm 0.73				218	2.65 \pm 0.78			
	NMF	275	4.31 \pm 0.70	2.21 \pm 0.78	[0.68; 3.74]	0.0047	184	5.74 \pm 0.79	3.09 \pm 0.92	[1.29; 4.89]	0.0008
SF-36 PCS score	PLA	268	0.52 \pm 0.45				218	1.12 \pm 0.47			
	NMF	275	1.61 \pm 0.43	1.09 \pm 0.48	[0.15; 2.03]	0.0232	184	2.35 \pm 0.48	1.23 \pm 0.55	[0.15; 2.31]	0.0259
EQ-5D Utility Index score	PLA	278	0.01 \pm 0.01				222	0.03 \pm 0.01			
	NMF	279	0.04 \pm 0.01	0.03 \pm 0.01	[0.01; 0.06]	0.0185	188	0.06 \pm 0.01	0.03 \pm 0.02	[0.00; 0.06]	0.0445
EQ-5D Health State score	PLA	274	2.43 \pm 1.10				221	3.13 \pm 1.19			
	NMF	276	5.18 \pm 1.07	2.75 \pm 1.17	[0.45; 5.05]	0.0191	189	6.60 \pm 1.20	3.46 \pm 1.38	[0.75; 6.17]	0.0124
DrInC Total score ^a	PLA	280	-11.95 \pm 1.23				226	-14.64 \pm 1.30			
	NMF	282	-13.25 \pm 1.20	-1.30 \pm 1.31	[-3.86; 1.26]	0.3200	189	-17.86 \pm 1.31	-3.22 \pm 1.47	[-6.12; -0.33]	0.0292

^a A lower score indicates fewer alcohol-related problems

DrInC, drinker inventory of consequences; **EQ-5D**, EuroQoL-5 dimensions; **MCS**, mental component summary; **MMRM** = Mixed Model Repeated Measures; **NMF** = nalmefene; **PCS**, physical component summary; **PLA** = placebo; **SF-36**, Short-Form health survey-36.

doi:10.1371/journal.pone.0129289.t002

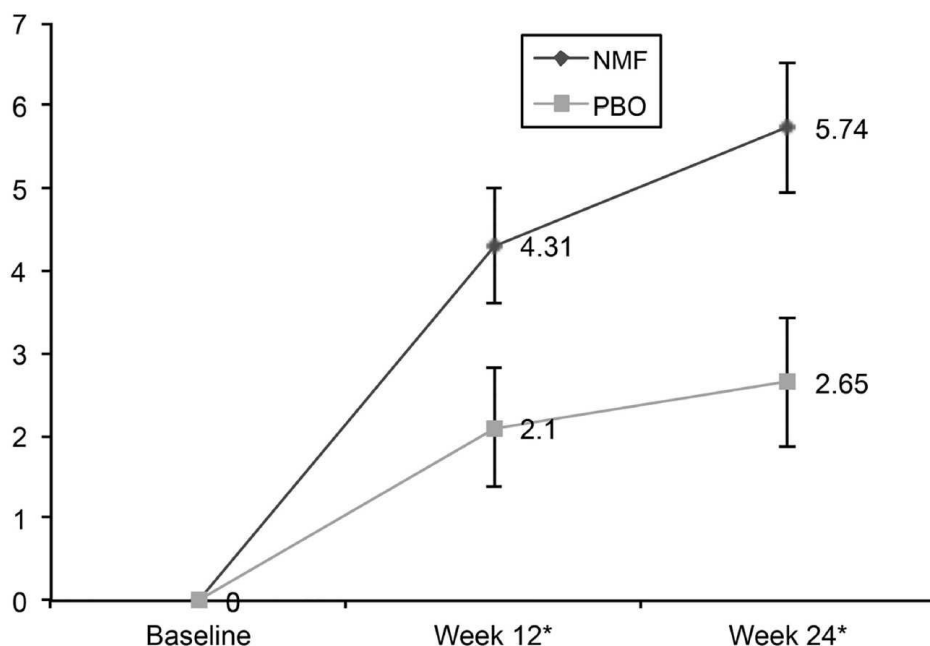


Fig 1. Adjusted mean change from baseline in SF-36 MCS Scores (mean ± SE). NMF, nalmefene; PBO, placebo; SF-36 MCS, Short-Form health survey-36 mental component summary. * $p < 0.05$.

doi:10.1371/journal.pone.0129289.g001

alcohol consumption ($r = -0.1811$; $p = 0.0003$) (Table 3). No such relationships were observed for EQ-5D utility index scores and changes in heavy drinking days and total alcohol consumption.

DrInC-2R total scores were improved to a greater extent by nalmefene than placebo, which is indicative of fewer alcohol-related problems, and the mean [95% CI] difference at 24 weeks was statistically significant (-3.22 [$-6.12, 0.33$]; $p = 0.0292$). The improvement in DrInC-2R

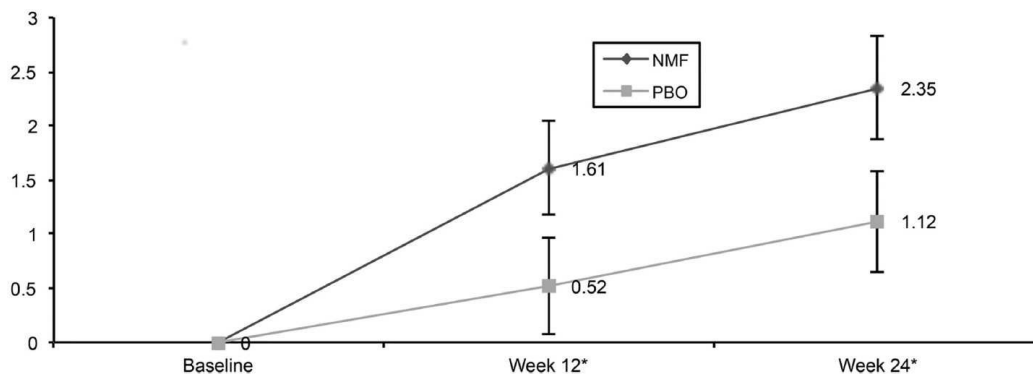


Fig 2. Adjusted mean change from baseline in SF-36 PCS Scores (mean ± SE). NMF, nalmefene; PBO, placebo; SF-36 PCS, Short-Form health survey-36 physical component summary. * $p < 0.05$.

doi:10.1371/journal.pone.0129289.g002

Table 3. Correlation coefficients for the relationship between changes from baseline to Week 24 in the number of monthly heavy drinking days (HDD) and monthly total alcohol consumption (TAC) versus changes in patient-reported outcome measures in the total population (nalmefene and placebo pooled data).

	HDD		TAC	
	Pearson Correlation Coefficient ^a	p-value	Pearson Correlation Coefficient ^a	p-value
SF-36 MCS score	-0.1941	<0.0001	-0.2061	<0.0001
SF-36 PCS score	-0.0569	0.2578	-0.0707	0.1596
EQ-5D Utility Index score	-0.0772	0.1217	-0.0761	0.1271
EQ-5D Health State score	-0.2023	<0.0001	-0.1811	0.0003
DrInC Total score	0.2046	<0.0001	0.2446	<0.0001

^a negative values indicate a positive correlation for QoL while positive values indicates a positive correlation for DrInC

DrInC, drinker inventory of consequences; **EQ-5D**, EuroQoL-5 dimensions; **MCS**, mental component summary; **PCS**, physical component summary; **SF-36**, Short-Form health survey-36; **VAS**, visual analogue scale.

doi:10.1371/journal.pone.0129289.t003

Table 4. Adjusted mean change from baseline to week 24 in SF-36 dimensions in patients with a high drinking risk level (MMRM, target efficacy population).

Short-Form health survey-36 (SF-36) Dimensions		Baseline		Change from Baseline to Week 12		Difference to Placebo			Change from Baseline to Week 24		Difference to Placebo		
		N	Mean ± SD	N	Mean ± SE	Mean ± SE	95% CI	p-value	N	Mean ± SE	Mean ± SE	95% CI	p-value
Bodily Pain	Placebo	319	49.16 ± 10.66	279	0.73 ± 0.67				226	1.47 ± 0.70			
	Nalmefene	316	49.85 ± 10.63	283	2.46 ± 0.66	1.73 ± 0.74	[0.28; 3.17]	0.0195	189	3.90 ± 0.72	2.43 ± 0.82	[0.82; 4.05]	0.0032
General Health	Placebo	318	43.84 ± 9.56	277	0.85 ± 0.56				224	1.46 ± 0.61			
	Nalmefene	318	44.71 ± 9.53	283	2.47 ± 0.54	1.62 ± 0.60	[0.45; 2.79]	0.0066	189	3.82 ± 0.62	2.36 ± 0.71	[0.96; 3.76]	0.0010
Mental Health	Placebo	319	41.97 ± 11.35	280	2.01 ± 0.66				226	1.82 ± 0.70			
	Nalmefene	316	41.66 ± 11.34	283	2.01 ± 0.66	1.61 ± 0.71	[0.21; 3.01]	0.0247	188	4.99 ± 0.72	3.17 ± 0.83	[1.54; 4.79]	0.0001
Physical Functioning	Placebo	317	50.95 ± 6.84	277	0.50 ± 0.43				223	1.03 ± 0.43			
	Nalmefene	318	51.01 ± 7.01	281	1.59 ± 0.42	1.09 ± 0.47	[0.16; 2.02]	0.0216	187	2.24 ± 0.44	1.21 ± 0.49	[0.24; 2.18]	0.0142
Role Emotional	Placebo	316	42.36 ± 11.40	274	0.67 ± 0.71				221	2.33 ± 0.75			
	Nalmefene	317	42.46 ± 11.46	280	3.25 ± 0.69	2.58 ± 0.77	[1.06; 4.10]	0.0009	188	4.66 ± 0.77	2.33 ± 0.89	[0.58; 4.08]	0.0093
Role Physical	Placebo	316	45.51 ± 9.2	273	0.94 ± 0.56				222	2.00 ± 0.60			
	Nalmefene	317	45.89 ± 9.34	281	2.64 ± 0.54	1.71 ± 0.60	[0.52; 2.89]	0.0048	188	3.36 ± 0.61	1.36 ± 0.71	[-0.04; 2.75]	0.0561
Social Functioning	Placebo	319	43.33 ± 11.95	280	3.93 ± 0.61				226	3.20 ± 0.67			
	Nalmefene	317	44.32 ± 10.62	284	2.09 ± 0.63	1.84 ± 0.69	[0.49; 3.19]	0.0078	189	5.36 ± 0.68	2.17 ± 0.79	[0.62; 3.71]	0.0061
Vitality	Placebo	319	47.04 ± 10.16	280	1.96 ± 0.60				226	1.97 ± 0.65			
	Nalmefene	319	47.48 ± 9.56	283	3.55 ± 0.58	1.59 ± 0.64	[0.33; 2.86]	0.0135	188	4.30 ± 0.66	2.34 ± 0.77	[0.83; 3.84]	0.0024

MMRM: mixed model repeated measures.

doi:10.1371/journal.pone.0129289.t004

total scores were significantly correlated to both a reduction in heavy drinking days ($r = 0.2046$; $p < 0.0001$) and total alcohol consumption ($r = 0.2446$; $p < 0.0001$) (Table 3).

Despite a reduction in the number of patients assessed at baseline, week 12 and week 24, there were no differences in baseline characteristics between patients who withdrew and patients who completed each study. Baseline characteristics and response to treatment for patients who withdrew and patients who completed each study were similar. Thus, there was no apparent missing-data mechanism. This applies to both the total population and to our *post-hoc* analysis population.

Discussion

The current *post hoc* analysis was designed to establish whether improvements in drinking behavior were associated with benefits in patient-reported outcomes for HRQoL and fewer alcohol-related problems. The assessment of HRQoL among alcohol-dependent subjects presents a number of challenges in the absence of a specific instrument developed specifically for alcohol dependence [13,22]. In this analysis we employed two instruments to monitor patient-reported outcomes related to HRQoL: SF-36 and EQ-5D. Compared with placebo, nalmefene produced significant improvements in HRQoL as assessed by patient-reported outcomes such as: SF-36 MCS, SF-36 PCS, 7 of 8 dimensions in the SF-36, EQ-5D utility index score and EQ-5D health state score. The only measure which did not achieve statistical significance was the 'role physical' dimension in SF-36 (mean difference versus placebo 1.36; $p = 0.0561$). At baseline the mean SF-36 MCS was 40.9 in both the placebo and nalmefene groups and this is markedly lower than the reference value for the U.S. general population. Interestingly, SF-36 PCS was over 50 at baseline in the two groups indicating that alcohol-dependent patients perceived their problems to be more psychological than physical. A similar finding was reported by Daepfen and colleagues in an early study using SF-36 to evaluate HRQoL in alcohol-dependent patients [38].

This analysis of patients with a high drinking risk level has confirmed significant patient-reported benefits in HRQoL with as-needed nalmefene in a controlled clinical comparison with placebo. Minimally Important mean group Differences (MIDs) in SF-36 scores (MCS, PCS, and the 8 domains) between the nalmefene and placebo groups were determined to assess whether the results were clinically meaningful. In our study the following MIDs were recorded: 3 for MCS, and mental health; and 2 for role-emotional, bodily pain, general health, social functioning and vitality. The greater improvements in HRQoL, with MIDs of 2–4, are clinically relevant from the patients' perspective [32]. Further, the improvement in EQ-5D utility index score for nalmefene versus placebo was similar to that observed in an observational longitudinal study in patients with alcohol dependence who shifted to lower alcohol consumption and fewer alcohol-related problems [20]. Unfortunately, the lack of published data regarding MIDs for the DrInC-2R scale precluded our ability to definitively associate clinical relevance to improved DrInC-2R scores. Nevertheless, the improvements in HRQoL found in the current study parallel significant reductions in heavy drinking days and total alcohol consumption reported in the same cohort [26].

This analysis also established a significant correlation between a reduction of alcohol intake (heavy drinking days and total alcohol consumption) and an improvement of HRQoL measures such as SF-36 MCS and EQ-5D health state scores, as well as total DrInC scores. A similar finding was previously reported in a naltrexone trial [39]. Even though the causal nature of the relationship between alcohol drinking reduction and HRQoL improvement cannot be inferred from the results of our study, this finding is an important contribution to the rationale for the "reduction concept" as a goal, in addition to the abstinence goal in the management of alcohol

dependence. The benefits in HRQoL are in addition to the reported reductions in all-cause mortality resulting from decreased alcohol consumption in heavy drinkers (defined as at least 60 g of alcohol per day in men or 40 g alcohol per day in women) [40,41].

This study has a number of limitations. Firstly, it was a *post hoc* analysis of patients with a high drinking risk level, rather than the total randomized population. However, as noted by van den Brink and colleagues, this reflects the behavior of patients pre-randomization, and the nalmefene and placebo groups were comparable in terms of numbers and baseline demographics/characteristics [26]. These patients are by definition at greater risk of alcohol-related harm and therefore represent the patients in most need of treatment. Another potential limitation relates to the original ESENSE 1 and 2 selection criteria which excluded patients with significant DSM-IV axis I co-morbidity and serious withdrawal symptoms, although this is in line with EMA guidelines for the development of pharmacological products for the treatment of alcohol dependence [10]. Other limitations of our study relate to the patient-reported outcomes used to gauge treatment effects on HRQoL. For example, the SF-36 questionnaire was administered every 3 months during the study; HRQoL may deteriorate during the first few weeks of treatment, and this would have been missed in the current study. In addition, SF-36 does not monitor problems with sleeping which can have a detrimental effect on HRQoL in alcohol-dependent individuals [18]. Furthermore, while SF-36 has been shown to be useful in alcohol-dependent subjects [38,42] it is nonetheless a generic health status measure, and is not based on specific symptoms associated with alcohol dependency. The information it collects may not be completely relevant or specific for alcohol-dependent subjects and it may not be the ideal HRQoL measure in this patient group [22]. However, as yet, no specific instrument has been developed to assess changes in HRQoL in alcohol-dependent patients [22]. With this in mind, a new HRQoL instrument which is specific to alcohol use disorder, namely the Alcohol Quality of Life Scale (AQoLS), is being developed and validated [22]. This instrument is currently available in English, French and Japanese language versions. Nevertheless, despite any potential shortcomings with using the generic SF-36 in patients with alcohol dependence, the HRQoL improvements observed in nalmefene-treated patients were significantly better than those achieved with placebo.

In conclusion, this analysis from two controlled clinical trials (ESENSE 1 and 2) demonstrated that nalmefene as-needed improved almost all patient-reported measures of HRQoL included in SF-36 and EQ-5D. These HRQoL gains paralleled significantly reduced drinking behavior as determined by reductions in heavy drinking days and total alcohol consumption, as well as fewer alcohol-related problems (as assessed by total DrInC-2R scores) [24–26]. While longer term experience is clearly needed, the move towards pharmacologically supported reductions in alcohol consumption, reduced health risk and improved HRQoL are highly desirable. Reduction rather than abstinence may be a more palatable treatment goal for patients with alcohol dependence, and an advance in this complex and difficult to manage therapeutic setting.

Acknowledgments

The authors thank Steve Clissold and David Figgitt, Content Ed Net, for providing valuable editorial support in the preparation of the article. The study was funded by Lundbeck and funding for editorial support was provided by Lundbeck SAS, France. Lundbeck has European marketing approval for Selincro (nalmefene).

Henri-Jean Aubin has received honoraria and travel grants from Lundbeck, Merck Serono, Ethypharm, D&A Pharma, Pfizer, and Bioprojet. Amandine Luquiens has received honoraria and travel grants from Lundbeck. Clément François, Nora Rahhali, Ylana Chalem, and Per

Sørensen are employees of Lundbeck. There are no further patents, products in development or marketed products to declare. This does not alter our adherence to all the PLOS ONE policies on sharing data and materials, as detailed online in the guide for authors.

Author Contributions

Conceived and designed the experiments: CF NR YC PS. Performed the experiments: CF NR YC PS AL HJA. Analyzed the data: NR YC PS. Contributed reagents/materials/analysis tools: CF NR HJA. Wrote the paper: CF NR HJA.

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Développement d'une échelle de qualité de vie spécifique du trouble d'usage d'alcool AQoLS (Luquiens et al. 2014)

Sur le constat précédemment décrit du besoin d'un instrument de type PRO mesurant la qualité de vie du point de vue du patient et spécifique du trouble d'usage d'alcool, nous avons entrepris de développer l'échelle Alcohol Quality of Life Scale (AQoLS) Notre but était de développer un instrument répondant à ces critères, en adoptant une méthodologie centrée sur le patient, c'est à dire en impliquant les patients dans la génération même des items, comme recommandé pour le développement d'instrument de type PRO. L'article qui suit décrit le développement de cette échelle.

Méthodes

Dans un but d'utilisation ultérieure transculturelle et pour éviter la génération d'items spécifique à un seul pays, l'échelle AQoLS a été développée d'emblée de manière bilingue, simultanément en France et en Angleterre.

Etape 1: développement d'une trame conceptuelle initiale hypothétique

La première étape de développement de l'échelle correspond à la constitution d'une trame conceptuelle initiale hypothétique à partir de la revue de la littérature précédemment décrite (Luquiens, Reynaud et al. 2012). Cette trame a permis d'élaborer un guide de discussion pour la conduite des groupes focus.

Etape 2: Groupes focus de patients avec un trouble d'usage d'alcool pour l'extraction du contenu du concept de qualité de vie

Le but de ces groupes était d'explorer du point de vue du patient l'impact du trouble d'usage d'alcool et de son traitement sur la qualité de vie du point de vue des patients. Les patients ont été sélectionnés pour leur hétérogénéité aussi bien en ce qui concerne les caractéristiques sociodémographique que sur l'histoire de leur trouble d'usage d'alcool

(trouble actuel ou en rémission, début tardif ou précoce). Les 38 patients inclus étaient invités à partager leur expérience personnelle de l'impact de l'alcool sur leur qualité de vie, et la discussion pouvait s'appuyer sur le guide élaboré lors de la première étape. Les discussions ont été enregistrées et retranscrites.

Etape 3: génération des items

Une analyse thématique a été réalisée sur les transcrits des groupes focus. Le codage des transcrits a été facilité par le logiciel de codage ATLAS.ti 6.2, permettant d'identifier les concepts pertinents pour les patients. Les concepts ont ensuite été organisés pour réviser la trame conceptuelle initiale, en s'appuyant sur les propos des patients. Cette trame a permis de générer un premier lot d'items en reprenant de façon extensive les formules utilisées par les patients pour rester au plus proche de leurs préoccupations.

Etape 4: revue d'experts

Le premier lot d'items a été soumis à la relecture d'experts pour une revue clinique pour s'assurer de leur pertinence. Une préoccupation particulière a été donnée pour éviter les formulations propres à un mode de consommation d'alcool, pour convenir notamment à l'abus d'alcool et à la dépendance. Les formules difficilement traductibles ont été évitées.

Etape 5: entretiens cognitifs de débriefing chez des patients avec un trouble d'usage d'alcool

Deux tours itératifs d'entretiens cognitifs ont été conduits en France et en Angleterre avec un nouvel échantillon de 31 patients, pour évaluer la validité de face et de contenu de la première version de l'échelle. Le premier tour avait pour but d'évaluer la bonne compréhension et l'acceptabilité des consignes, items, options de réponse et de la période de rappel. Des modifications pouvaient alors être apportées pour améliorer la version initiale de AQoLS. Le deuxième tour avait pour but de tester les changements réalisés après le premier tour.

Résultats

Etape 1: trame conceptuelle initiale

Cinq domaines principaux avaient été extraits de la revue de la littérature présentée précédemment: les relations interpersonnelles (conjoint, famille, amis), les activités (loisirs, sociales, tâches ménagères et travail), prendre soin de soi (apparence, appétit, santé), et impact psychologique (humeur, stress, joie, énergie, motivation, et concentration), et conditions de vie (finances et logement).

Etape 2: Groupes focus de patients avec un trouble d'usage d'alcool pour l'extraction du contenu du concept de qualité de vie

Echantillon de patients

Six groupes focus ont été conduits en Angleterre auprès d'un total de 17 patients sur le site du Royal Liverpool and Broadgreen University Hospital Trust). Quatre groupes focus ont été conduits en France auprès de 9 patients à l'hôpital Paul Brousse à Villejuif, et 12 patients au Centre Hospitalier Universitaire in Clermont-Ferrand. Les patients inclus étaient tous alcoolodépendants, car les patients ayant un abus d'alcool ne s'étaient finalement pas présentés au groupe focus. Les patients avaient entre 23 et 69 ans, un tiers était des femmes. 57% des patients français et 47% des patient anglais avaient un trouble actuel. Le nombre de verres pour un jour typique de prise d'alcool allait de 3 à plus de 10.

Analyse thématique des transcrits des groupes focus

L'analyse de contenu a permis d'identifier 7 domaines clés impactés par le trouble d'usage d'alcool, servant de base pour le développement de la trame conceptuelle révisée et de structure hypothétique pour AQoLS : relations interpersonnelles, prendre soin de soi, impact émotionnel, contrôle, conditions de vie, sommeil. La saturation a été atteinte dans chaque pays. Ces domaines faisaient partie de la trame initiale à l'exception du contrôle. Le domaine du contrôle concernait aussi bien la restriction de liberté que constituait l'alcool, dictant les actions que la perte du contrôle de son comportement dans les autres domaines,

notamment lors des alcoolisations. La figure 1 représente la trame conceptuelle révisée après les focus groupes, représentée graphiquement. Les sept domaines clés correspondent à la structure hypothétique de l'échelle AQoLS.

Etape 3: génération des items

Un pool initial de 90 items a d'abord été réduit à 68 items en tenant compte des redondances, les items flous se référant à plusieurs concepts, et les items ne concernant potentiellement qu'une catégorie restreinte de patients.

Une échelle de Likert à 4 points a été choisie pour graduer l'intensité des réponses, et une période de rappel de 2 semaines choisie dans un premier temps.

Etape 4:

Le pool réduit de 68 items a été réduit à 50 items après la revue des experts: 20 items retirés car peu pertinents cliniquement ou difficilement traductibles, 23 ont été révisés dans leur formulation, et 2 ont été ajoutés.

Etape 5: Entretiens cognitifs de débriefing

31 patients ont participé à des entretiens individuels. Les patients présentaient une alcoolodépendance actuelle ou en rémission, sauf un patient qui présentait un abus d'alcool. Après le premier tour d'entretiens auprès de 16 patients, 14 items ont été retirés, car considérées comme flous, ambigus, difficile à comprendre ou trop extrême. 2 ont été combinés et 7 ont été révisés dans leur formulation. 4 items supplémentaires ont été ajoutés portant sur l'agressivité, les capacités physiques, les loisirs, le malaise physique, sur la suggestion des patients. Le pool révisé de 39 items a été retesté dans un deuxième tour d'entretiens, permettant de redéfinir la période de rappel à 4 semaines pour faciliter l'évaluation des patients, reformuler 3 items et retirer 5 items qui restaient ambigus.

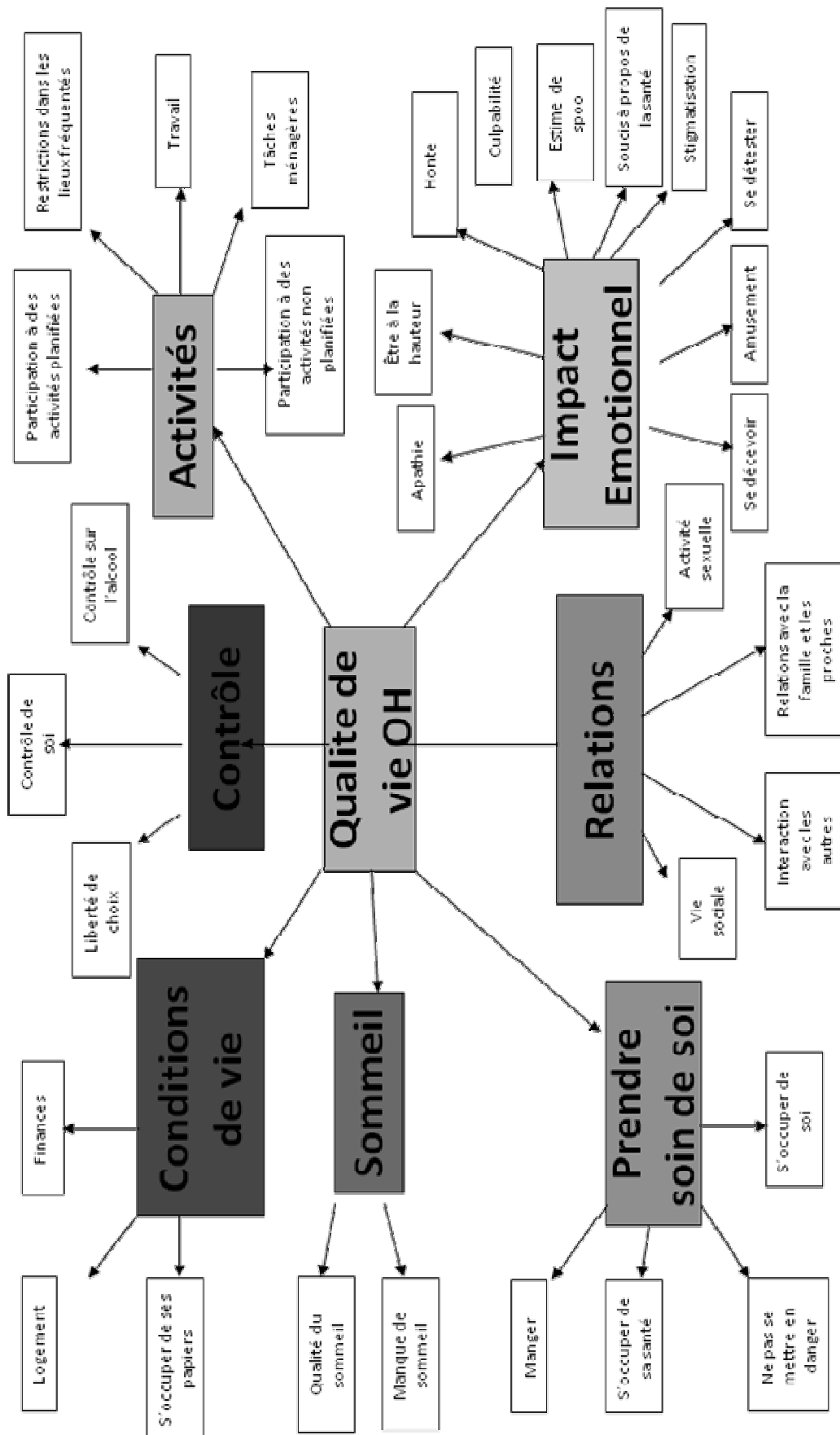
Discussion

Le développement d'AQoLS a permis par sa méthode centrée sur le patient d'obtenir une échelle de 34 items pertinents et acceptables du point de vue du patient. Son développement bilingue permet de limiter le risque d'avoir généré des items difficilement traductibles et culturo-dépendant. Des patients avec différents profils de consommation ont contribué au développement de l'échelle AQoLS, cependant un seul patient abuseur a pu être inclus. AQoLS présente une structure hypothétique constituée de 7 domaines. Le domaine du contrôle n'avait jamais été inclus dans un instrument de qualité de vie. Il paraît particulièrement intéressant d'avoir identifié ce domaine du point de vue du patient qu'il est habituellement considéré comme le symptôme principal de l'addiction et la fonction cognitive la plus perturbée dans l'addiction du point de vue des experts (Gan, Guevara et al. 2014). L'évaluation subjective par les patients de l'intensité de l'impact de l'alcool sur ce domaine comme partie de la qualité de vie semble donc particulièrement pertinent cliniquement.

Le développement de l'échelle AQoLS a permis de montrer son excellente validité de face et de contenu. Il reste à ce stade nécessaire d'explorer la structure de l'instrument pour valider l'hypothèse des 7 dimensions proposées, ainsi que de renseigner de ses propriétés psychométriques et sa validité de construit dans les populations cibles, et en particulier chez les patients présentant un abus d'alcool.

Versions française et anglaise de AQoLS: voir Annexes 1 et 2

Figure 1: Trame conceptuelle révisée issue des groupes focus (OH= alcool)



Development of the Alcohol Quality of Life Scale (AQoLS): a new patient-reported outcome measure to assess health-related quality of life in alcohol use disorder

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Accepted: 10 November 2014
© Springer International Publishing Switzerland 2014

Abstract

Purpose The development of patient-centred approaches and of reduction in consumption strategies in alcohol use disorder requires giving a larger place to qualitative assessments that are closer to patients' concerns and more clinically relevant than drinking outcomes and generic health-related quality of life instrument. Our purpose was to develop from patients input the Alcohol Quality of Life Scale (AQoLS), a disease-specific measure for alcohol use disorder (AUD).

Methods Concept elicitation focus groups were conducted with AUD patients in the UK and France. Thematic analysis was used to identify key areas of impact of AUD, and draft items were developed to capture these issues. The

draft items underwent expert review to ensure clinical and cross-cultural applicability. Two iterative rounds of cognitive debriefing interviews were conducted with AUD patients in both countries, to assess face and content validity.

Results From focus groups conducted with 38 AUD patients, seven areas of impact emerged, forming the basis for the AQoLS: relationships, activities, looking after self, emotional impact, control, living conditions, and sleep. An initial pool of 90 items was reduced to 50 following the review process. In cognitive interviews, the measure took less than 10 min to complete, and patients reported that items were relevant to their experience. Following Round 1 interviews ($n = 16$), 14 items were removed because patients felt they were unclear or uneasy to respond to, 2 were combined, 7 were revised, and 4 new items were added. The recall period of 2 weeks was changed to 4 weeks, based on patient comments. Following Round 2

Electronic supplementary material The online version of this article (doi:10.1007/s11136-014-0865-7) contains supplementary material, which is available to authorized users.

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interviews ($n = 15$), 5 items were removed and 3 were modified to produce the 34-item AQoLS.

Conclusion As the only de novo measure of health-related quality of life developed specifically for AUD, the AQoLS offers the potential of increased sensitivity to show the effectiveness of therapeutic interventions from the patient's perspective.

Keywords Quality of life · Alcohol use disorder · Patient-reported outcome · Focus groups · Health-related quality of life

Introduction

Alcohol use disorders (AUDs) affect an estimated 76.3 million people worldwide and is associated with 2.5 million deaths annually [1, 2]. AUDs care is evolving in a complex context: the integration of successful harm reduction strategies imported from the illegal substance use disorders field and the increasing use of patient-centred approaches, challenging this still stigmatizing area of health care. While the use of alcohol reduction strategies is liable to reduce the huge treatment gap and to avoid contradictory strategies among patients with codependence, a number of specialists nevertheless only offer abstinence-oriented programs. Some may experience difficult cross-discipline pressures in serving patients with AUDs and other comorbid conditions. Abstinence has long been a key therapeutic goal in the treatment of alcohol dependence [3]. However, clinical practice now also focuses on the benefits of reducing patient alcohol intake without necessarily achieving abstinence. This is reflected in the recent European approval of nalmefene, an opioid-receptor antagonist that is taken on an as-needed basis to reduce alcohol consumption in alcohol-dependent patients.

This evolution of AUDs treatment leads to the development of additional outcomes to traditional drinking measures, which are clinically more relevant and closer to patients concerns. Clinical trials commonly focus on assessments of quantity of alcohol consumed or the number of days of abstinence (or number of days of excessive drinking) as a primary endpoint [4]. However, such assessments are not considered relevant in clinical practice; alcohol specialists deem them to be poor predictors of treatment success [5]. These assessments also poorly reflect changes observed in patients who follow a nonlinear and complex disease course, changing their drinking patterns over time [6]. The change in paradigm integrating the reduction in consumption in alcohol use disorder requires one to give a higher place to qualitative assessments that are closer to patients' concerns and more relevant clinically.

AUDs are complex conditions affecting medical, psychological, and social domains. Alcohol dependence is a leading cause of impairments in overall health-related quality of life (HRQOL), general health, mental and physical health, and social functioning [7]. Quality of life is recognized as an important area to consider in assessing individuals with alcohol use disorders and in assessing alcoholism treatment outcome [8–10] and, in a recent survey of alcohol specialists in France, was considered to be the most important criterion for treatment success [5]. The literature demonstrates the utility of using QoL measures throughout assessment and treatment as a motivational tool and as a marker for treatment efficacy [11].

HRQOL instruments explore patients' perceptions of the impact of a particular disease on their lives [12]. General QoL instruments explore overall quality of life independently of any health condition. This type of QoL instrument is thought to be less robust and less sensitive to change than health-related QoL instruments. Responsiveness, also called sensitivity to change, is required from a HRQOL instrument, particularly to be used in clinical trials. Definitions of responsiveness differ in the kind of change that a responsive instrument should be able to detect, namely clinically important changes over time, changes due to treatment effects, or changes in the true value of the underlying construct. It is accepted that a good evaluative HRQL instrument should be able to measure minimal important clinical changes in specific HRQL domains over time. This minimal change should not be a property of the instrument, but should be defined before each study, and should be determined from the patient perspective for a PRO [13]. Health-related quality of life (HRQOL) is often included as a secondary endpoint in clinical trials, reflecting patients' feelings and functioning and the impact of their health condition beyond simple symptom assessment [14].

Currently, there is only one disease-specific HRQOL instrument for alcohol dependence, the AIQoL 9 [15]. However, this measure was developed from the generic Short-Form Health Survey-36 (SF-36), without patient input [16]. A systematic review published in 2012 revealed that eight HRQOL instruments, all of which were generic, had been used in 18 randomized, controlled trials of alcohol dependence [10]. However, despite six of the trials showing positive treatment effects, only one trial demonstrated a significant HRQOL difference between intervention and control groups [10].

These findings highlight the need for a disease-specific instrument to assess HRQOL in AUDs, developed from patients input. The aim of the current study was to develop the Alcohol Quality of Life Scale (AQoLS), a new instrument to measure HRQOL in AUDs.

Methods

Stages in the development of the AQoLS

To avoid any country-specific characteristic of the new measure, all developmental stages of the AQoLS were conducted simultaneously in the UK and France.

Stage 1: Development of the initial conceptual framework

The study adopted the European Medicines Agency definition of HRQOL: “the patient’s subjective perception of the impact of his disease and its treatment(s) on his daily life, physical, psychological and social functioning and well-being” [16]. Using this definition, the initial, hypothesized, conceptual framework for the AQoLS was developed from a previous systematic review of HRQOL instruments conducted by the first author [10]. A discussion guide for the running of the focus groups relied on this framework to help exploration of potential HRQOL concepts in the concept elicitation stage.

Stage 2: Concept elicitation focus groups with AUDs patients

The purpose of the focus groups was to explore the impact of AUDs and its treatment from a patient perspective. The group discussions were facilitated by trained interviewers in each country (authors DW, LD, and SC in the UK and NH and JP in France) and were audio-recorded and transcribed. Focus groups are semi-structured discussions that aim to explore a specific set of issues. Interviewers commenced the focus group by asking broad questions about their history of alcohol use disorder, before asking focal questions on the impact of their alcohol consumption on their quality of life [17]. The hypothesized, conceptual framework formed the basis of a discussion guide used to conduct the concept elicitation focus group sessions with AUDs patients in the UK and France sites. Each group was structured around this discussion guide constructed to explore the concepts of interest in the initial conceptual framework and to identify any further areas of impact not currently captured. Although participants individually answered the facilitator’s questions, they were encouraged to talk and interact with each other. This technique is built on the notion that the group interaction encourages respondents to explore and clarify individual and shared perspectives [17].

Stage 3: Generation of items for the AQoLS

Transcripts from the focus groups in the UK and France were subjected to thematic analysis, facilitated by the

coding software ATLAS.ti 6.2 (Scientific Software Development; Berlin), to identify the HRQOL concepts relevant to patients. Analysis of the data was conducted independently in each country (authors DW, LD, and SC in the UK and NH and JP in France). Coding for qualitative data, which means selecting significant sections from participant statements, was performed on each transcript by two researchers. The findings from the analyses were integrated into a revised conceptual framework. Draft AQoLS items were formulated initially in UK English and translated in French, to reflect each concept in the revised framework, using patients’ own words first from the UK focus groups and then from the French group, as much as possible.

Stage 4: Expert review

The draft items underwent expert review, including a clinical review (by authors AL, HJA, and LO), to ensure the clinical relevance of the items. The clinicians evaluated whether the draft items would be sensitive to the likely impact of reduced alcohol consumption, and the impact of alcohol abuse as well as dependence.

A translatability assessment of the draft items was conducted simultaneously with the clinical review. The assessment, undertaken by professional translators, focused on identifying items that would pose difficulties for future cultural adaptation. After this review, items were modified or removed, and an initial version of the AQoLS in UK English was produced. This version was used to generate the initial French version, again using patients’ own words from the French focus groups wherever possible.

Stage 5: Cognitive debriefing interviews with AUDs patients

Two iterative rounds of face-to-face, cognitive debriefing interviews were conducted with a new sample of 31 other AUDs patients ($n = 17$ in UK and $n = 14$ in France), to revise the draft AQoLS and to evaluate face and content validity. The Round 1 interviews were designed to evaluate the interpretation and acceptability of the instructions, items, response options, and recall period and to make any necessary revisions ($n = 16$). The Round 2 interviews were designed to test the changes made after Round 1 and to confirm that the revised measure was acceptable to patients and assessed the intended concepts appropriately and comprehensively ($n = 15$). For each round, patients completed the draft AQoLS in the presence of an interviewer and then were asked a series of questions to assess their understanding and perceptions of each instruction, item, and response option. The interviews were conducted by

trained interviewers in each country (authors DW, LD, and SC in the UK and NH and JP in France).

Patients and setting

Patients in the UK were recruited through the Royal Liverpool and Broadgreen University Hospital Trust Alcohol Services. Patients in France were recruited through the Centre d'Addictologie of the Hôpital Paul-Brousse in Villejuif, and the Centre Médico-Psychologique B of the Centre Hospitalier Universitaire in Clermont-Ferrand. In- and out-patients with alcohol use disorder from these three sites were proposed purposively to enter the study by telephone or face-to-face contact. Reasons for refusing to enter the study were justified by a lack of available time for most patients by clinician impression, even if no flow chart has been conducted on the non-included patients.

Patients meeting diagnostic criteria of current or remitted alcohol abuse or dependence, as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) and assessed with the Mini-International Neuropsychiatric Interview (MINI 6.0) [18], were recruited into the study. Additional inclusion and exclusion criteria ensured that patients would be able to engage with the research process and excluded significant comorbidities or treatments that might confound the exploration of the HRQOL impact of AUDs (see Box S1).

The focus groups were configured to ensure variation in the sample characteristics, while maintaining some homogeneity within groups to facilitate discussion and disclosure. Care was taken to recruit patients with a variety of demographic and disease characteristics, including patients with abuse and dependence in terms of DSM-IV criteria, current and remitted patients, and patients with late and early age of onset per Babor's typology [19]. Thus, the groups were stratified by age of onset of alcohol abuse or dependence, aged 25 years or younger versus above 25 years, in reference to Babor classification, to insure to represent all possible patients profiles in terms of temperament and personal history. Our methodology relies on the concern of maximizing the responsiveness potential of the instrument: (1) the focus groups were stratified by alcohol abuse or dependence course status, namely current versus remitted; this stratification should help to cover all possible fields impacted by alcohol consumption, and particularly those changing over time and with a change of alcohol consumption pattern. (2) Patients included in focus groups were asked during discussion to mention fields that have change with their previous changes of alcohol consumption pattern.

Results

Development of the initial conceptual framework (Stage 1)

Five principal HRQOL concepts were identified from the systematic literature review: relationships (partner, family, and friends), activities (hobbies, social, household jobs, and work), looking after self (appearance, appetite, and health), psychological impact (mood, stress, happiness, energy, motivation, and concentration), and living conditions (finances and housing). These concepts formed the basis of the discussion guide for the concept elicitation focus groups, with additional open-ended prompts to identify new concepts raised by patients.

Concept elicitation focus groups with AUD patients (Stage 2)

Patient sample

Six focus groups were conducted in the UK, with a total of 17 patients. Four focus groups were conducted in France (9 in Villejuif and 12 in Clermont-Ferrand), with a total of 21 patients. The demographic and disease characteristics of the focus group sample are presented in Table 1. The combined concept elicitation sample represented a range in terms of sociodemographic characteristics, alcohol-dependence severity, and AUD status, namely current versus remitted. However, the clinical sites were unable to recruit any patients with abuse (in the absence of dependence). Patient's age ranged from 23 to 69 years old. One-third of the sample was female. The patients with alcohol dependence represented a range in dependence severity from mild to severe. The number of dependence criteria varied in a range of 3–7. The number of drinks in a typical drinking day in patients included in the focus groups varied from 3 to "more than 10 drinks". Time since first contact with health services varies from 1 day to 20 years in the UK groups and from 1 month to 17 years in the French groups.

Findings from the focus groups

AUD was described as an all-consuming and overwhelmingly destructive experience, permeating almost every aspect of life. For many patients, the once pleasurable and sociable activity of drinking alcohol had taken over their lives, destroyed relationships, and undermined feelings of self-worth. Some differences in the experiences of patients in the UK and France were identified. Patients in the UK placed greater emphasis on the behavioural consequences of their drinking and were more likely to engage in solitary

Table 1 Characteristics of the focus groups patient sample

Characteristic	UK (n = 17)	France (n = 21)
Age (years)		
Median (IQR)	42(38–52)	48(42–50)
Range	23–65	31–69
Sex [n (%)]		
Male	12 (70.6)	14 (66.7)
Female	5 (29.4)	7 (33.3)
Relationship status [n (%)]		
Married or living as	3 (17.6)	10 (47.6)
Not married or living as	14 (82.4)	11 (52.4)
Employment status [n (%)]		
Working	5 (29.4)	11 (52.4)
Not working	12 (70.6)	10 (47.6)
DSM-IV diagnosis [n (%)] ^a		
Dependence	17 (100)	21 (100)
Abuse	0 (0)	0 (0)
MINI dependence score ^b		
Median (IQR)	6 (5–7)	5 (4–6)
Range	4/7–7/7	3/7–7/7
AUD status [n (%)]		
Current	8 (47.1)	12 (57.1)
Remitted	9 (52.9)	9 (42.9)
Number of drinks on a typical occasion [n (%)]		
3–4	0 (0)	2 (10)
5–6	3 (18)	6 (29)
>6	12 (70)	13 (62)
Frequency of having 6 or more drinks on one occasion over last year [n (%)]		
Weekly	1 (6)	7 (33)
Daily or almost daily	13 (76)	14 (67)
Time since first contact with health services (years) (mean, sd)	4.5 (5.9)	5.7 (5.8)

AUD alcohol use disorder, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, *MINI* Mini-International Neuropsychiatric Interview, *IQR* interquartile range

^a DSM-IV dependence and abuse criteria assessed by the Mini-International Neuropsychiatric Interview 6.0 (14). Patients received a diagnosis of alcohol dependence if they met a minimum of three out of seven dependence criteria. If the criteria for dependence were not met, the patient was assessed according to four abuse criteria; a minimum score of 2 was required for a diagnosis of abuse

^b MINI dependence score is the number of dependence criteria met; scores can range from 0 to 7, with a minimum of 3 required for a diagnosis of alcohol dependence

drinking than patients in France. Patients in France described greater negative social consequences of abstinence.

Thematic content analysis of the focus group transcripts identified seven key areas of impact of AUD, which formed the basis of the revised conceptual

framework for the AQoLS (Fig. 1): relationships, activities, looking after self, emotional impact, control, living conditions, and sleep. The areas identified were captured in the initial conceptual framework developed from the literature, with the exception of control. Saturation was reached across the focus groups within each of the two countries, confirming that the sample size of the focus groups is acceptable. The identified areas of impact are described briefly as follows.

Relationships

“... and there are others that I’ve truly hurt, things that I’ve done to them, things I’m not even aware that I’ve said to them because I can’t even remember anymore.” [France-Group 3_Remitted AUD]

Patients described the impact of alcohol on how they behaved towards the people around them and the consequences that had on their relationships. Common experiences were breakdowns in trust and communication and damaged social, family, and intimate relationships.

Activities

“Because of your timetabling your life around it, it’s difficult to make plans and follow it through.” [UK-Group 2_Current AUD]

Patients in the focus groups described the restrictions they encountered (whether self-imposed or otherwise) on their engagement in family, social, household, and work activities. Common experiences were missed special events, being unable or unwilling to participate in activities with family and friends, not being able to do things at short notice, neglecting household tasks, and being unable to work or performing poorly at work.

Looking after self

“I’ve run myself that much into the ground.” [UK-Group 2_Current AUD]

For some patients, the all-consuming nature of their drinking had consequences for their interest in and ability to take care of themselves. Risk-taking or harmful behaviour was commonly described: driving while under the influence of alcohol, fighting, and disregarding personal safety. As alcohol took a stronger hold, patients described neglecting their appearance and failing to attend to health matters. Patients also described erratic eating; for some, this took the form of overeating or eating “the wrong thing”, whereas others neglected or became physically unable to eat.

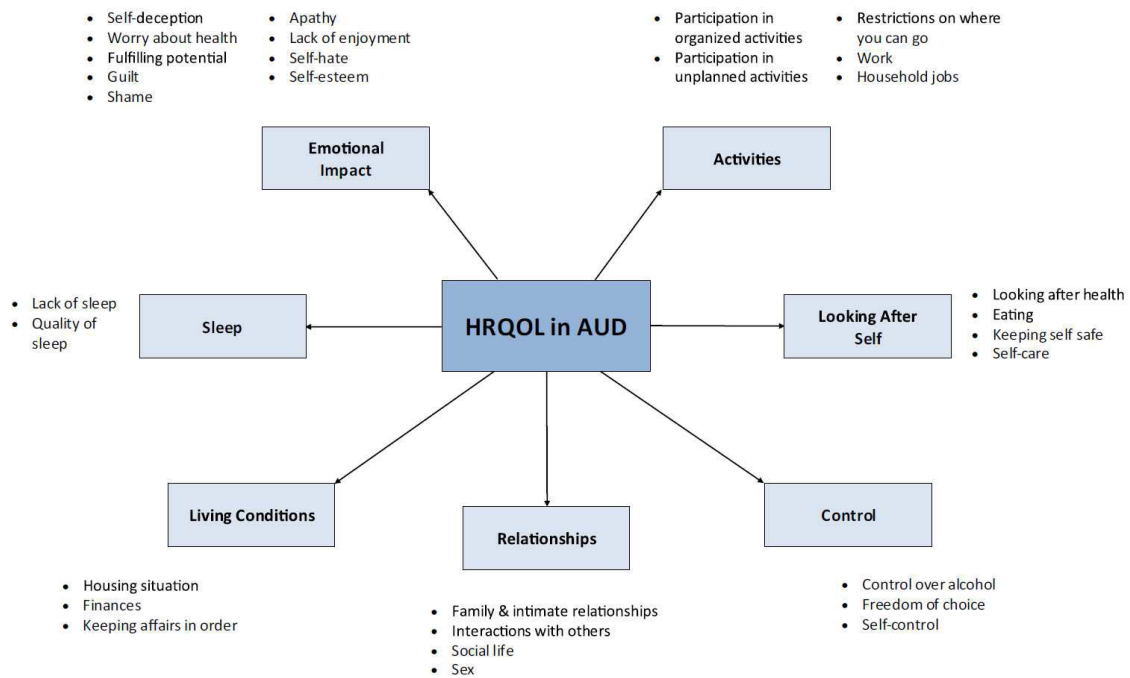


Fig. 1 Conceptual framework for the assessment of health-related quality of life (HRQOL) in alcohol use disorder (AUD)

Emotional impact

“When we look into a mirror, I mean, it becomes hard, hard, almost impossible!” [France-Group 2_Current AUD]

Patients expressed a range of emotions in relation to their drinking, many of which contributed to a vicious cycle of drinking; alcohol-generated emotions that led the individual to drink more to forget. Common feelings were guilt, shame, embarrassment, self-hate, apathy, and the absence of enjoyment.

Control

“In those moments you realize that you are the slave of [alcohol].” [France-Group 3_Remitted AUD]

Patients considered alcohol to be a physical entity that had the power to dictate their actions and behaviours. They described an existence dominated by alcohol, either through its consumption in periods of drinking or through its avoidance during abstinence. Alcohol restricted freedom of choice and brought a loss of self-control.

Living conditions

“I was given some money when I was dismissed [from paid employment], and I drank my way

through that. And then I had to put the house on the market.” [UK-Group 2_Current AUD]

Patients described the financial cost of AUD, particularly individuals who were unable to find or sustain employment. Some patients, particularly those in the UK, had experienced financial difficulties or lost their home due to non-payment of bills and loans. Many described using any spare money to buy alcohol, leaving nothing to spend on themselves or their family. Patients also described neglecting the organizational aspects of their lives, such as opening and dealing with mail or paying bills on time.

Sleep

“It didn’t matter how much I drank, I could drink bucket loads and I still couldn’t sleep.” [UK-Group 4_Remitted AUD]

Disturbed sleep was a major concern for a number of patients. Patients described difficulties getting to sleep and staying asleep, disrupted sleeping patterns, and the inability to sleep.

Generation of items for the AQoLS (Stage 3)

Draft items for the new HRQOL instrument were generated to reflect each of the issues represented in the revised

conceptual framework. The initial pool of 90 items was reduced to 68 by removing duplicate items, items expressing multiple concepts, and items potentially not relevant to all potential respondents.

A 4-point Likert-type response scale (“not at all”, “a little”, “quite a lot”, and “very much”) was selected to balance responder burden and the potential measurement sensitivity of the items. We chose the use of four points as opposed to five, thus eliminating neutral mid-points and forcing the respondents to make a choice. However, 4-point response scales could show more ceiling and floor effects. Ceiling and floor effects will then have to be carefully explored in a future validation. A recall period of between 2 and 4 weeks was considered to be most appropriate to reflect the nature of the disorder and the relative stability of the HRQOL concepts captured within the AQoLS, while allowing scope to detect changes in HRQOL over time. A 2-week recall was selected for initial testing.

Expert review (Stage 4)

The reduced pool of 68 items was subjected to expert review for clinical relevance by the clinical teams in the UK and France and for translatability by the professional translators. As a result of these reviews, 20 items were removed and 23 items were revised. Two new items were added, relating to social belonging and worry about the impact of alcohol on the individual's life. These changes resulted in a revised set of 50 items, which were then tested in the cognitive debriefing interviews.

Cognitive debriefing interviews with AUD patients (Stage 5)

Patient sample

Seventeen patients with AUD took part in the cognitive debriefing interviews in the UK (9 in Round 1 and 8 in Round 2) and 14 took part in France (7 in each round). Table 2 presents the characteristics of the patient sample. Overall, there was a range of different demographic and disease characteristics. The exception was in relation to DSM-IV diagnosis, with only 1 patient meeting the MINI 6.0 criteria for alcohol abuse. The subjects who gave themselves over to the cognitive interviews were balanced in terms of age of onset of the alcohol use disorder. Age of onset varied from 13 to 60 years old in the UK cognitive interviews and from 10 to 39 years old in the French cognitive interviews. Time since first contact with health services varied from 1 month to 18 years in the UK interviews and from 3 months to 23 years in the French interviews.

Patients in the first round of interviews in both countries found the questionnaire items easy to understand and complete. Patients reported that the majority of items were relevant to their experiences with alcohol. Items were considered for removal if patients described the items as unclear, ambiguous, or overlapping in content with other items. After the Round 1 interviews, the following changes were made: 14 items that were considered redundant, ambiguous, difficult to understand, irrelevant, overly extreme, or otherwise problematic were removed; 2 items considered similar were combined into 1 item; and 7 items were revised to improve acceptability, phrasing, or clarity of meaning. Patients also identified four issues not included in the measure: poor behaviour, ability to do physical activities, pursuit of hobbies, and physical discomfort. New items were added to address these issues. Changes also were made to the layout and verb tense of the UK items, to address a tendency for patients to disregard the 2-week recall period.

The revised 39-item AQoLS was tested in Round 2. After five Round 2 interviews in the UK, it was clear that the difficulties associated with the recall period had not been resolved. Some patients commented that they could not relate some items to “the last 2 weeks” and suggested that a longer time period would be more suitable. To address these comments, a longer recall period, of 4 weeks, was tested in the remaining three UK interviews and in the French interviews and was found to work well.

Patients in both countries found the revised questionnaire easy to understand and complete, and they considered the items to be relevant to their experiences with alcohol. Patients took less than 10 min to complete the questionnaire (range UK, 3–9 min and France, 4–10 min). As a result of patients' comments in Round 2, minor revisions were made to three items to further clarify meaning, and five items that were considered ambiguous or irrelevant were removed. These changes resulted in the final 34 items of the AQoLS, which are listed in Table 3, together with the corresponding hypothesized domains.

Discussion

Development of the AQoLS

The AQoLS is the first *de novo* measure of HRQOL developed specifically for use in AUDs. The content was developed and refined with extensive patient input, through focus group discussions and cognitive debriefing interviews. The measure includes patients' own words wherever possible. Such patient-centred methods ensure that the final 34 items of the AQoLS are relevant and acceptable to all potential respondents.

Table 2 Characteristics of the cognitive debriefing interview sample

Characteristic	Round 1		Round 2	
	UK (n = 9)	France (n = 7)	UK (n = 8)	France (n = 7)
Age (years)				
Median (IQR)	46 (40–47)	40 (36.5–52.5)	49.5 (40–51.75)	55 (46.5–55)
Range	29–51	32–57	30–72	41–57
Sex [n (%)]				
Male	7 (77.8)	5 (71.4)	5 (62.5)	5 (71.4)
Female	2 (22.2)	2 (28.6)	3 (37.5)	2 (28.6)
Relationship status [n (%)]				
Married or living as	3 (33.3)	3 (42.9)	3 (37.5)	3 (42.9)
Not married or living as	6 (66.7)	4 (57.1)	5 (62.5)	4 (57.1)
Employment status [n (%)]				
Working	2 (22.2)	6 (85.7)	2 (25.0)	4 (57.1)
Not working	7 (77.8)	1 (14.3)	6 (75.0)	3 (42.9)
DSM-IV diagnosis [n (%)] ^a				
Dependence	9 (100)	6 (85.7)	8 (100)	7 (100)
Abuse	0 (0)	1 (14.3)	0 (0)	0 (0)
MINI dependence score ^b				
Median (IQR)	5 (3–6)	6 (4.5–6)	6 (5.75–7)	5 (4–6.5)
Range	3–7	4–7	4–7	3–7
Current AUD status [n (%)]				
Current	6 (66.7)	3 (42.9)	6 (75.0)	5 (71.4)
Remitted	3 (33.3)	4 (57.1)	2 (25.0)	2 (28.6)
Number of drinks on a typical occasion [n (%)]				
1–2		1		1
3–4				1
5–6	6	1	7	2
>6	2	3	1	3
Time since first contact with health services (years) (mean, sd)	3.9 (6.0)	3.1 (2.6)	7.7 (6.5)	5.2 (8.0)

AUD alcohol use disorder, DSM-IV Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, MINI Mini-International Neuropsychiatric Interview, IQR interquartile range

^a DSM-IV dependence and abuse criteria assessed by the Mini-International Neuropsychiatric Interview 6.0 (14). Patients received a diagnosis of alcohol dependence if they met a minimum of three out of seven dependence criteria. If the criteria for dependence were not met, the patient was assessed according to four abuse criteria; a minimum score of 2 was required for a diagnosis of abuse
^b MINI dependence score is the number of dependence criteria met; scores can range from 0 to 7, with a minimum of 3 required for a diagnosis of alcohol dependence

The parallel development in the UK and France of the instrument and the incorporation of a translatability assessment into the development process allowed avoiding any country-specific aspect of the items of the new instrument. The inclusion of items of relevance to different cultures and the removal of concepts that could pose difficulties for translation will help to facilitate future language adaptations of the AQoLS.

The instrument development process represented a collaborative partnership between clinical academics, patient-reported outcomes (PRO) experts, and industry representatives. The study used best practice methods in PRO measurement to produce an instrument that would be suitable for assessing HRQOL in alcohol research and in clinical trials of new products to treat AUDs. As the first truly disease-specific HRQOL measure for AUDs, the AQoLS offers the potential of increased sensitivity to assess treatment efficacy in clinical trials, compared to that

provided by generic instruments (9). The development methodology followed industry-recognized standards for PRO instruments used in clinical trials [20], including an iterative process for deriving the underlying conceptual framework and extensive patient input throughout the development process to ensure content validity. Particularly, in focus groups, qualitative cognitive interviewing ensures understanding and completeness of the concepts contained in the items [20].

Patients with different patterns of AUDs contributed to the development of the AQoLS, including both current and remitted patients and patients with different levels of severity. This approach is concordant with the new DSM-5 criteria, which considers AUDs as a single diagnosis comprising mild, moderate, and severe disorder [21]. The AQoLS therefore is applicable to the spectrum of AUD and to patients in different stages of the disorder, helping to ensure sensitivity to change. However, only one patient

Table 3 Items and hypothesized domains of the 34-item AQoLS

Hypothesized domain	Item
Activities	I have felt I miss out on everyday activities with family and friends
	It has been difficult for me to follow through on plans
	I have been restricted in the places I can go because of alcohol
	I have struggled doing physical activities due to alcohol (e.g. DIY, walking, cycling)
	It has been too much effort to do jobs around the house due to alcohol (e.g. cleaning, gardening, maintaining the house)
Relationships	Alcohol has interfered with my ability to work
	I have cut myself off from other people
	I have neglected the people close to me
	Alcohol has damaged my close relationships
	I have behaved badly towards other people
	I have felt I miss out on family life because of alcohol
	I have felt that people have no trust in me
Living conditions	Alcohol has interfered with my sex life
	Alcohol has interfered with my relationships with friends
	I have struggled to keep on top of my everyday household affairs (e.g. dealing with mail, organizing appointments)
	Alcohol has had a negative effect on my housing situation
Emotional impact	All my money has gone on alcohol
	Alcohol has caused me financial difficulties
	I have felt ashamed of myself
	I have felt that people look down on me
	I have felt that I am wasting my life
Looking after self	I have worried about the effect alcohol has been having on my health
	I have worried about alcohol causing problems in my life
	I have had no appetite
	I have neglected my appearance
Control	I have neglected my general health
	I have put myself in risky situations
	I have felt that nothing matters more than alcohol
	Alcohol has controlled me
	My life has revolved around alcohol
Sleep	I have planned my days around alcohol
	I have felt as though I have not been in control of myself
	I have not had a good night's sleep
	I have not been getting enough sleep

AQoLS Alcohol Quality of Life Scale

met the diagnostic criteria for alcohol abuse according to DSM-IV criteria, and thus, the applicability of the AQoLS for patients with the mildest AUDs severity has not been proven. Nonetheless, consideration was given to the inclusion of a range of items in terms of severity, and specific attention was given to this issue during the clinical review of the draft items.

Content of the AQoLS

The AQoLS assesses the impact of AUDs over seven hypothesized HRQOL domains: relationships, activities, looking after self, emotional impact, control, living conditions, and sleep. Previous HRQOL instruments used in AUDs do not assess control [10], yet control was a consistent and significant issue for patients in this study. Loss of control is often a key reason for seeking treatment, and regaining control over alcohol consumption could be a preferred therapeutic goal for many patients [5, 22, 23]. Control also has been described as the core cognitive dysfunction in addictive behaviours [24]. Moreover, the switch from controlled to compulsive drug-seeking behaviour represents a significant shift in the underlying neurological processes related to drug-seeking and drug-taking behaviours [25]. It is not clear whether control dysfunction is a precursor or a consequence of addiction, but there is evidence to support its reversibility following remission [26]. The assessment of control through the AQoLS could provide valuable patient-reported information in future studies.

Further validation of the AQoLS

The AQoLS has been shown to have excellent face and content validity through cognitive debriefing interviews with patients. It remains necessary to verify the dimensional structure of the instrument and establish its psychometric properties in terms of reliability (test-retest and internal consistency), construct validity (known groups and convergent/divergent), and responsiveness.

Study limitations

This article reports the development of the AQOLS, and a validation study is under way and needed to explore the generalizability and the psychometric properties of the scale.

Difficulties with recruitment and non-attendance of patients at prearranged focus group sessions meant that a number of groups, particularly those in the UK, contained fewer participants than anticipated. However, we observed

no detrimental effects on the dynamics of group discussions nor on the quality of the data obtained.

The clinical sites experienced problems in recruiting patients meeting the MINI 6.0 DSM-IV criteria for alcohol abuse. The reason for this is unclear, but is likely related to the nature of the patient population, who are potentially hard to identify through health services and may be reluctant to engage in research. Only one patient with alcohol abuse, who took part in the Round 1 cognitive debriefing interview in France, was recruited for this study. While this individual's assessment of the instrument did not differ from that of other patients, the validity of the AQoLS for alcohol abuse patients must be further explored.

Since our scale has been developed to fulfil a lack of specific instrument to be used in clinical trials among patients with alcohol use disorders, its properties should be explored in the future in populations with comorbidities. AQoLS could show some limits in its use in ecological studies with broad inclusion criteria.

Conclusion

The AQoLS is the first de novo measure of HRQOL developed specifically for use in AUDs. The instrument has 34 items, is quick and easy for patients to complete, and has been shown to have excellent face and content validity. By focusing on the HRQOL domains of relevance to AUDs patients, the AQoLS offers the potential of increased sensitivity to show the effectiveness of therapeutic interventions from the patient's perspective. Further validation is needed to confirm the hypothesized dimensional structure of the measure and to establish its psychometric properties.

Acknowledgments Lundbeck SAS founded this study. RTI Health Solutions (RTI-HS) has been commissioned by Lundbeck SAS (France) to undertake this study in the UK and France.

Conflicts of interest AL has received sponsorship to attend scientific meetings from Lundbeck. PL is an employee of Lundbeck. DW, SC, LD, and MP are employees of RTI Health Solutions. NH and JD are employees of Creativ-Ceutical. RTI Health Solutions and Creativ-Ceutical received funding from Lundbeck for the conduct of this study. PML has received the following: Educational grants for research, honoraria, and travel support for activities as a consultant/advisor and lecturer/faculty member for the following pharmaceutical companies: Astra-Zeneca, Bristol Myers Squibb, Eli Lilly, Janssen, Lundbeck, Roche, Sanofi, and Servier. Consultant/scientific advisor/speaking engagements and has served on advisory boards for Astra-Zeneca, Janssen, Lundbeck, Otsuka, Roche, and Takeda. Consultant in clinical trials for Amgen, Astra-Zeneca, Lundbeck, Roche, and Sunovion. HJA has received sponsorship to attend scientific meetings, speaker honoraria, and consultancy fees from Bioprojet, D&A Pharma, Ethypharm, Lundbeck, Merck-Serono, Novartis, and Pfizer. LO received an educational grant for attendance at a scientific meeting from Lundbeck for participation in the study. In addition, LO

reports the following: Personal pecuniary interest: LO has provided clinical expertise to a number of organizations, including independent research, management, and industry companies. Most recently, LO has performed the following work: Was a member of a medical expert steering group sponsored by Lundbeck for the development of a local integrated care pathway for the prevention and management of alcohol use disorders in adults. This work has been accredited by the Royal College of General Practitioners (RCGP), Alcohol Concern, and Substance Misuse Management in General Practice (SMMGP). This work was supported by travel expenses and honoraria to attend meetings. Received sponsorship from Lundbeck to attend scientific meetings (ESBRA, and EPA), including travel, accommodation, and subsistence. Received sponsorship from Lundbeck to present at scientific meetings, including travel and honoraria to cover reasonable expenses. Personal family interest: None. Non-personal pecuniary interest: Lundbeck has provided a research grant to a clinical supervisor to investigate predictive factors leading to alcohol-related health care utilization. Personal non-pecuniary interest: None.

Ethical standard Prior to initiation of the study, the study protocol was subjected to human ethics and research review by the relevant authorities in the UK and France. In the UK, NHS ethics approval was granted by the National Research Ethics Service Committee North West—Liverpool East (REC Ref. 12/NW/0322). Local research and development (R&D) approval also was granted from the Royal Liverpool and Broadgreen University Hospital NHS Trust (R&D No. 4328). In France, approval for the study was obtained from the Committee for the Protection of Persons (Comité de Protection des Personnes [CPP]) and the competent authority, the French Agency for the Medical Safety of Health Products (Agence Française de Sécurité Sanitaire des Produits de Santé [AFSSAPS]). Review and approval of contracting documents for use with physicians were obtained from the National Council of Physicians (Conseil National de l'Ordre [CNO]), and hospital agreements were obtained. The study was also reviewed and granted approval from one of the institutional review boards (IRBs) of RTI International (IRB No. 13074). Each patient signed a consent form to enter the study, after having been given an information notice on the study protocol.

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La qualité de vie du point de vue des patients alcoolodépendants : un impact similaire entre la France et l'Angleterre malgré des habitudes de consommations différentes. (Luquiens et al. en préparation)

L'article «Luquiens, A., L. Owens, et al. ([DRAFT]). "Quality of life in alcohol dependence: similar cross-cultural impact beyond specific drinking habits."» préparé pour soumission en anglais est ici synthétisé en français, puis inséré dans sa version complète en anglais.

Introduction

Comme précisé précédemment, notre initiative centrée sur le patient pour explorer la qualité de vie dans le trouble d'usage d'alcool est la première de ce type à notre connaissance. Or il apparaît important de mieux définir le poids de l'alcool d'un point de vue de santé publique, non seulement en matière de coût directs (morbidity, mortalité, hospitalisation, perte de productivité par les arrêts de travail, criminalité principalement) (Rehm, Patra et al. 2010; Laramee, Kusel et al. 2013), mais aussi en matière de coûts indirects. En effet, certains auteurs considèrent qu'il pourrait y avoir une sous-estimation de ces coûts liée à la difficulté de mesurer les coûts humains. Les coûts humains sont définis par l'impact d'une maladie sur la qualité de vie d'une personne et de sa famille. Certains auteurs ont tenté d'estimer ces coûts en étudiant l'altération de la qualité de vie liée à des pathologies compliquant l'alcoolodépendance (Jeanrenaud, Priez et al. 2003). Il n'existe pas à notre connaissance de documentation des coûts humains relatifs à la qualité de vie liée au trouble d'usage d'alcool en dehors de l'évaluation d'un gain en valeurs utiles après une intervention thérapeutique (Laramee, Brodtkorb et al. 2014). De plus, la compréhension qu'un patient a de sa maladie est influencée par sa culture (Kleinman, Eisenberg et al. 1978). Les groupes focus présentés précédemment et ayant permis de développer l'échelle AQoLS ont eu lieu en

France et en Angleterre. L'article ici présenté est une seconde analyse qualitative de ces groupes dont le but est de confirmer le contenu du concept de QVLS dans l'alcoolodépendance du point de vue des patients, identifié lors du développement de AQoLS, et d'explorer toute différence socioculturelle de ce contenu entre les patients anglais et français.

Méthodes

L'échantillon de patients a été décrit précédemment. Il est important de préciser que les patients anglais étaient hospitalisés pour un autre motif que l'alcool, et sont donc considéré pour le sujet comme non chercheurs de soins vis à vis de leur trouble d'usage d'alcool, contrairement aux patients français qui étaient pris en charge pour un trouble d'usage d'alcool actuel ou en rémission.

Deux corpus ont été construits en rassemblant d'une part les groupes focus français, et d'autre part les groupes focus anglais. Les corpus ont été mis au format compatible avec le logiciel d'analyse qualitative ALCESTE 2015. Ce logiciel a été utilisé pour assister à l'analyse et à l'interprétation de chaque corpus séparément. ALCESTE conduit une analyse lexicale hiérarchique descendante. Cette analyse est basée sur la co-occurrence de mots dans des segments de texte dans le but de synthétiser et d'organiser les informations essentielles suivant 5 étapes (Mazzonetto and Fiates 2014): (1) la segmentation du texte et le codage du texte: le corpus est segmenté en Unités de contexte élémentaires (UCE), supposés contenir une idée caractéristique. (2) Lemmatisation: les mots sont réduits à leur radicaux et classés comme "analysables" (noms, verbes, adjectifs, adverbes...) ou "supplémentaires" (prépositions, pronoms...). (3) définition d'une table de contingence des formes réduites analysées et des unités des UCE (4) classification hiérarchique descendante permettant d'obtenir des classes stables et leurs mots significatifs (test du Khi-2) (5) Description des classes pour aider l'interprétation, notamment à l'aide d'analyse en cluster de chaque classe.

L'association entre les classes et le statut (actuel, en rémission, groupe mixte) du trouble d'usage d'alcool a été testée par le test du khi-2 dans chaque corpus.

Résultats

38 patients alcoolodépendants ont été inclus en France et en Angleterre.

Le nombre de classes stables était de trois en France et de cinq en Angleterre

Description des classes issues de la classification descendante hiérarchique dans chaque corpus

Les deux corpus étaient organisés autour de trois thèmes principaux, correspondants aux trois classes françaises, et quatre des cinq classes anglaises: cœur de l'impact sur la qualité de vie (classes 1), se procurer et consommer de l'alcool (classes 2), sources d'aides et dispense des soins (classe 3 dans le corpus français, et classes 4 et 5 dans le corpus anglais). Dans le corpus anglais, une classe supplémentaire indépendante décrivait l'impact sur les conditions physiques (classe 3).

Cœur de l'impact sur la qualité de vie (classe 1)

La classe 1 dans les deux corpus détaille l'impact des consommations d'alcool sur la qualité de vie. Les patients des deux corpus rapporte la sensation douloureuse de devenir une autre personne lorsqu'ils boivent. Huit domaines principaux communs y sont détaillés par les patients des deux pays: (1) les relations avec les proches, (2) les émotions négatives , en particulier la culpabilité, l'anxiété et la dépression, (3) l'estime de soi effondrée, (4) le désinvestissement des activités et le manque de perspectives, (5) l'impression que la vie entière tourne autour de l'alcool (6) la perte du contrôle comportemental, (7) les troubles cognitifs, (8) la dégradation des conditions de vie. Les patients en rémission ont plus contribué à la classe 1 que ceux ayant un trouble d'usage d'alcool actuel, alors qu'en France ce sont ceux avec un trouble actuel qui ont le plus contribué à renseigner le cœur de l'impact de l'alcool sur la qualité de vie.

Se procurer et consommer de l'alcool (classe 2)

La classe 2 dans les deux corpus décrit les alcoolisations. On a retrouvé des différences dans les habitudes de consommations, notamment avec une plus grande variété d'alcools, la mention de pratique du binge drinking et l'achat dans des magasins dédiés en Angleterre.

Aide (classes 3 française et 4 et 5 anglaises)

Le corpus français rapporté par des patients en soins alcoologiques fait plus référence à une aide médicalisée et le corpus anglais rapporté par des patients non chercheurs de soins pour l'alcool, plus à des groupes d'entraide.

Impact physique (classe 3 anglaise)

Les patients anglais non en soins alcoologiques ont évoqué aussi bien des symptômes d'intoxication que des symptômes de sevrage.

Discussion

Le corpus a mis en évidence des différences importantes dans la façon de se procurer et de consommer de l'alcool. Les trois thèmes communs malgré ces confirment l'hypothèse d'un contenu transculturel de la qualité de vie.

Certains de ces domaines évoqués sont des domaines explorés par des échelles génériques de QVLS: les relations avec les proches, les émotions négatives. D'autres n'étaient pas explorés comme partie de la qualité de vie : l'estime de soi effondrée, le manque de perspective et le désinvestissement des activités, vivre l'alcool comme une contrainte, la perte du contrôle comportemental et les troubles cognitifs. Certains de ces domaines étaient explorés par d'autres échelles explorant d'autres concepts que la qualité de vie. Certains de ces domaines étaient considérés du point de vue de l'expert comme des facteurs de risque ou des marqueurs de la toxicité de l'alcool. L'approche centrée sur le patient permet la réconciliation de la perspective de l'expert et de celle du patient. Tous ces domaines ont été intégrés dans l'échelle AQoLS sauf les troubles cognitifs.

Certaines des différences observées comme la description des sources d'aide et la contribution différente des patients en rémission ou non entre les deux pays, pourraient s'expliquer plutôt par le statut de chercheur de soins ou non, vis-à-vis de l'alcool. Savoir identifier spontanément l'impact de l'alcool sur la qualité de vie pourrait faire partie du processus de soins. Ce dernier point pourrait être confirmé par un recrutement de populations plus proches entre les deux pays. En effet, les conditions différentes de recrutement entre la France et l'Angleterre constituent une limite à l'étude.

Quality of life in alcohol dependence: similar cross-cultural impact beyond specific drinking habits [DRAFT]

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ABSTRACT

Context

This study is the first patient-centered initiative to describe how quality of life is affected by an alcohol use disorder. The aim of this study is to identify the content of quality of life related to alcohol use disorder and to explore any socio-cultural differences between France and UK in quality of life impact of alcohol use disorder, from the patient perspective.

Methods

We included 38 patients with current or remitted alcohol dependence in France and in UK to take part to focus groups on the impact of alcohol consumption on quality of life. The focus groups were transcribed into 2 corpuses. The French and the English corpuses were qualitatively analyzed using ALCESTE software to identify and describe classes of content. Association between classes and AUD status (current/remitted/mixed group) were performed (chi-2 test) in both corpuses.

Results

The number of stable classes was 3 in the French corpus and 5 the English one. Three main shared themes composed the corpuses: impact on quality of life, alcohol obtaining and consumption, and sources of help. Content of impacted quality of life by alcohol was similar between the two countries. Patients gave particular salience on degraded self-esteem, loss of behavioral control and cognitive difficulties. Main differences between the two corpuses were (1) the division of the third theme in two areas in the English corpus, namely institutional sources of help and help from relatives, (2) an additional theme in the English corpus reporting physical impairment, mostly withdrawal symptoms (3) cultural differences in alcohol obtaining and consumption.

Conclusion

Despite differences in drinking habits, the domains of life impacted by alcohol identified by the patients were similar across the two countries and are then confirmed to be non-country-specific. Moreover, the help-seeking status could impact the ability in spontaneously identifying impacted-by-alcohol domains of life.

INTRODUCTION

The high burden of alcohol has been well described from a public health perspective, in terms of morbidity/mortality (Rehm, Mathers et al. 2009; Rehm and Roerecke 2013). Costs and avoidable costs of excessive alcohol consumption have also been estimated, mainly through productivity loss, followed by health care (i.e. hospitalization and medication) (Laramee, Kusel et al. 2013), and criminality (Rehm, Patra et al. 2010). Some authors suggested an under-estimation of these social costs due to the difficulty in assessing human costs (Jeanrenaud, Priez et al. 2003), including harm to others (Nutt, King et al. 2010). Human costs are usually defined as the impact on the patient's and his family's quality of life. Health-related Quality of life (HRQOL) is defined as "the patient's subjective perception of the impact of his disease and its treatment(s) on his daily life, physical, psychological and social functioning and well-being" (EMEA 2005). An attempt to estimate human cost used impact on health related quality of life of four physical illnesses attributable to alcohol consumption (Jeanrenaud, Priez et al. 2003). No documentation of human cost relative to health-related quality of life of alcohol use disorder is available, except in terms of change after a therapeutic intervention (Laramee, Kusel et al. 2013; Laramee, Brodtkorb et al. 2014). Moreover, until recently, health related quality of life was assessed in patients with alcohol use disorder using generic scales, with a potential loss of information due to low specificity and irrelevance of some of the content of these scales (Luquiens, Reynaud et al. 2012). Particularly, the physical component of generic scales seems insufficiently specific and poorly sensitive to change. In fact, these scales, although mostly self-questionnaires, have been developed from the expert's perspective, and did not involve patients during the items generation process (Luquiens and Aubin 2014). However, patient input is required in the development process of a patient reported outcome (FDA 2009). Patient's input in health care providing and decision making in terms of therapeutic strategies are the basis of patient-centered approaches and is recommended by most health administrations including the Food and Drug Administration (Patel 2012). To our knowledge, this is the first patient-

centered initiative to describe quality of life in alcohol use disorders. This initiative led to the development of a patient reported outcome specifically designed to assess quality of life in alcohol use disorders, the Alcohol Quality of Life Scale (AQoLS) (Luquiens, Whalley et al. 2014). Kleinman demonstrated in the 70's how a patient's culture influences the understanding of illness and the identifying of the impact of illness (Kleinman, Eisenberg et al. 1978). It is therefore interesting to explore quality of life in different cultural contexts. The aim of this study is to identify the content of quality of life related to alcohol use disorder and to explore any socio-cultural differences in QoL content and impact of alcohol use disorder, from the patient perspective.

METHODS

Sample

Patients in the UK were non-treatment-seekers regarding alcohol, recruited through the Royal Liverpool and Broadgreen University Hospital, where they were hospitalized for another reason but alcohol use disorder. Patients in France were treatment-seekers recruited through the Centre d'Addictologie of the Hôpital Paul-Brousse in Villejuif, and the Centre Médico-Psychologique B of the Centre Hospitalier Universitaire in Clermont-Ferrand. In- and out-patients with an alcohol use disorder from these three sites were proposed purposively to enter the study by telephone or face-to-face contact. Reasons for refusing to enter the study were justified by a lack of available time for most patients by clinician impression, even if no flow chart has been conducted on the non-included patients. Patients meeting diagnostic criteria of current or remitted alcohol abuse or dependence, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and assessed with the Mini-International Neuropsychiatric Interview (MINI 6.0), were recruited into the study. Additional inclusion and exclusion criteria ensured that patients would be able to engage with the research process and excluded significant comorbidities or treatments that might confound the exploration of the HRQOL impact of AUDs: Inclusion criteria were : (1) Patient meets the

clinical diagnostic criteria of current or remitted (remitted for between 1 and 12 months) alcohol abuse (minimum of 1 criteria met) or dependence (minimum of 3 criteria met), as defined by DSM-IV and assessed with the Mini-International Neuropsychiatric Interview (MINI 6.0) (2) Patient is aged 18 years or older (3) Patient has the cognitive ability to participate in a focus group or cognitive debriefing interview (as judged by the clinical team) (4) Patient is able to provide written informed consent. Exclusion criteria were: (1) Patient has learning difficulties that prevent him/her reading and responding to questionnaires (2) Patient has a major physical comorbidity judged by the clinical team to be a significant influence on the patient's day-to-day life (e.g., liver failure) (3) Patient has another axis 1 diagnosis (with the exception of nicotine dependence) (4) Patient is judged by the clinical team to be incapable of participating in the study (e.g., if the patient is unable to give fully informed consent) (5) Patient is currently taking baclofen for alcohol dependence (in the lack of documentation of a possible high rate of imputable side effects and level of incapacity (ANSM 2014)) (6) Patient is currently undergoing acute withdrawal treatment (7) Patient has significant cognitive impairment, as judged by the clinical team and, for participants in the cognitive debriefing interviews, evaluated with the Mini-Mental State Examination (MMSE).

Focus groups

The purpose of the focus groups was to explore the impact on quality of life of AUDs and its treatment, from a patient perspective. The group discussions were facilitated by trained interviewers in each country (authors DW, LD, and SC in the UK and NH and JP in France) and were audio-recorded and transcribed. Focus groups are semi-structured discussions that aim to explore a specific set of issues. Interviewers commenced the focus group by asking broad questions about participants history of alcohol use disorder, before asking focal questions on the impact of their alcohol consumption on their quality of life (Tong, Sainsbury et al. 2007). A discussion guide was constructed to explore the concepts of interest identified in the literature, namely in a systematic review of quality of life (Luquiens, Reynaud et al. 2012) and to identify any further areas of impact not currently considered as part of quality of

life related to alcohol use disorder. This guide was used to conduct the concept elicitation during the focus group sessions with AUDs patients in the UK and France sites.

Data analysis

After verbatim transcription of the recordings from the focus groups, the moderator reviewed the transcripts, assembled them in two corpuses, French and English. The corpuses were organized according to Alceste software (ALCESTE, V. 2015, Image, Toulouse, France) requirements. Alceste was used to assist in data analysis and interpretation of each corpus separately. Alceste conducts lexical analysis using the descending hierarchical classification method. It is based on calculations made about the co-occurrence of words in segments of text with the aim of synthesizing and organizing essential information in a textual database. It operates in the following five stages: (1) Text segmentation and word coding: the corpus is segmented into elementary units of context (EUCs), which are text segments that contain a characteristic idea. The words are classified using an internal dictionary (French dictionary for the French corpus, and English dictionary for the English corpus); (2) Lemmatization: the words are reduced to their radicals and classified as “analyzable” (nouns, verbs, adjectives, adverbs, etc.) or “supplementary” (prepositions, pronouns, etc.); (3) Definition of a contingency table of “analyzable” reduced forms and elementary units of context (EUCs); (4) Top-down hierarchical classification analysis: performed to obtain stable classes and their significant words (tested by chi-square); (5) Class description to aid interpretation. The significant vocabulary of each class, that is, the words which give sense to the classes, was selected based on the concomitant occurrence of the following criteria: (1) Higher than average frequency of occurrences in the corpus; (2) Class association, determined by a chi-square value (χ^2) above 3.84 ($gI = 1$, indicating that the reliability of association between the word and the class is greater than 95%). Elementary Units of Contexts (EUCs) significantly associated to the classes were also identified based on a chi-square value above 3.84. EUCs are segments of text that contain a characteristic idea or a meaning. One of the researchers attending the French focus groups in one of the centers interpreted the results

based both on the significant words and on the significant EUCs of each class. The chi-square value associating words and EUCs to the classes enabled the interpretation of the classes' meanings, allowing the researcher to grasp the ideas that define each of them. To understand the content of the classes, the researcher must locate the significant words of each class on the significant EUCs (Mazzonetto and Fiates 2014). Cluster analyses of each class were performed. Association between classes and AUD status (current/remitted/mixed group) were performed (chi-2 test) in both corpuses.

RESULTS

Characteristics of the samples are presented in table 1. We included 38 patients with current or remitted alcohol dependence in France and in UK.

Characteristics of the corpuses

The total number of forms was 33522 and 85132, the number of distinct forms was 2968 and 3943, the number of stable classes was 3 and 5, and the percentage of EUCs classified was 60 and 67%, respectively in the French and the English corpuses.

Description of classes for the top-down hierarchical classification analysis in French and in English corpuses

The two corpuses were organized around three main topics, corresponding to the three French classes, and four of the English classes: core impact on quality of life (class 1), alcohol obtaining and consumption (class 2), sources of help and health care providing (class 3 in the French corpus, classes 4 and 5 in the English corpus). In the English corpus, there is an additional independent class referring to physical impairment (class 3). The figures 1 and 2 present the dendrograms from top-down hierarchical classification analysis of the classes and major associated words.

Core impact on quality of life (class 1)

The class1 in the 2 corpuses details the core of impact on quality of life of alcohol consumption. Patients reported loss and degradation in many domains of their life, and suffered from the feeling of turning into a different person while drinking. The table 2 gives examples of EUCs from the English corpus. All impacted domains are common between the French and the English corpuses: (1) relationships with family and friends, (2) negative emotions, namely guilt, anxiety, depression, (3) the low self-esteem, (4) the disinvested activities included sexuality and the lack of perspective and projects, (5) the feeling that life is scheduled by alcohol consumption and living alcohol as a constraint, (6) the loss of behavioral control leading for instance to violent talks or fights, (7) memory and cognitive impairment, (8) the degradation of living conditions (namely through loss of work, of a flat, financial difficulties). Cognitive impairment and deficits in memory have been identified as close to loss of behavioral control in French patients in the cluster analysis of the class 1, but this association was not observed in the English class 1 (associated to the same node n°2, supplementary online only figure 1 and 2). However, quotations from the English corpus show that patients have identified the same link: EUC n° 1875 : " well initially I feel great and then I drink that much that I can't remember really, honestly. yeah, I have memory issues but the thing is I say things to people and I can be absolutely horrible and I mean really horrible but I can't remember what I say."

In UK, patients with Remitted AUD contributed significantly more to class 1 than patients with current AUD. Opposite results were observed in France.

Alcohol obtaining and consumption (Class 2)

Class 2 in the English and French corpuses describes the drinking occasions, from the alcohol obtaining to the consumption itself, and all the organization required enabling the drinking occasions. Drinking is presented in both corpuses as a very strict routine. It refers to

the kind of alcohol, the time and place of obtaining and the horary restrictions, and the time and place of drinking if different from the obtaining one. The description is very rich and precise in the 2 Corpuses, with the highest percentage of EUCs classed (respectively 54% and 29% in the French and in the English corpuses). Socio-cultural similarities are the importance of the evening and night time as preferred moments to drink alcohol. In the French corpus, the way from work to home is a risky situation to drink. In both corpuses, the house can be either a consumption place or a shelter place to avoid drinking. Concomitant use of tobacco is also reported in both corpuses in this class. Differences are a wider variety of alcohol drunked in the English corpus, and the places of obtaining, linked to local alcohol selling legislation. In UK, patients frequently buy alcohol in dedicated shops, (i.e.off-licence, “offy”), which is not reported by the French patients. Last, Binge drinking is reported by English patients but not by French patients.

Sources of Help (French class3 and English class 4 and 5)

The French class 3 is composed of verbatim borrowed from health care providers, namely technical words (e.g. “anxiolytic”, “factor”, “psychologist” “self-confidence”, “medication”), used concomitantly to motivational components, routinely used among the French investigator centers (e.g. “so much better”, “to realize”). In the English corpus among non-treatment seeking regarding alcohol patients, two close classes refer to help. The class 4 refers to mutual support groups, more than to health care obtaining; the verbatim is composed of negative emotions (e.g. “shame”, guilt) and a redemption-like process (e.g. “admit”, “sorry”). The class 5 refers to help from relatives, but also to the burden of a difficult personal history, especially poor emotional support.

Physical impairment (English class 3)

Interestingly, we observed in the English corpus an additional class relative to physical impairment, separated from the class 1 relative to the impact of alcohol on quality of life. This

class reports mostly withdrawal symptoms, like shaking, sleep disorder, digestive troubles, anxiety, but also intoxication symptoms, like fatigue and loss of energy.

DISCUSSION

Three main themes were shared by The French and English corpuses :core impact on quality of life, alcohol obtaining and consumption, and sources of help. Content of impacted quality of life by alcohol was similar between the two countries. Main differences between the two corpuses are (1) the division of the third theme in two areas in the English corpus, namely institutional sources of help and help from relatives, (2) an additional theme in the English corpus reporting physical impairment, mostly withdrawal symptoms (3) cultural differences in alcohol obtaining and consumption.

Different drinking habits between UK and France appear in our study: different place and horary for obtaining alcohol and binge drinking evocation in UK. The first one is highly influenced by different alcohol selling legislation (Assemblée_nationale and Sénat 2009; Home_Office 2015), with more constraining horary restriction in the UK. Different drinking patterns and particularly high amount of alcohol per drinking occasion and binge drinking have previously been described as more frequent in UK than in France (Kuntsche, Rehm et al. 2004; Dunbar and Crombie 2011). These differences in drinking habits support the relevance of our corpuses.

Despite differences in the drinking habits, the domains of life impacted by alcohol identified by the patients were similar across the two countries. Some of those domains are explored by generic HRQOL scales: relationships with family and friends, and negative emotions. However others could have been incompletely explored: guilt is not usually explored, or even not explored at all in HRQOL scales. These usually unexplored domains, like low self-esteem, disinvested activities included sexuality the lack of perspective and projects, feeling that life is scheduled by alcohol consumption and living alcohol as a constraint, loss of behavioral control leading (for instance to violent talks or fights), memory and cognitive impairment, living conditions impairment (namely through loss of work, of a flat, financial

difficulties) are relatively specific to alcohol mental and alcohol use disorders. Some of these domains have been previously explored in scales exploring the consequences related to alcohol consumption (Miller and Longabaugh 1995). If the domains can overlap, the way of assessment totally differs because these consequences scales are expert-centered and are usually not self-questionnaires. One should take into account the possible stigma influencing the expert-reported outcomes, whereas alcohol use disorder is one of the conditions the most impacted by stigma among health care providers (Ronzani, Higgins-Biddle et al. 2009; Stuart 2012). Memory deficits, cognitive impairment and loss of behavioral control are till today perceived by health care providers like traits, risks factor of addiction or markers of alcohol toxicity, more than a patient complaint (Blume, Schmaling et al. 2005; Gan, Guevara et al. 2014). This patient-centered approach allows a conciliation between the observed by the expert symptoms and patients' asking for change. These domains are identical to those included in the AQoLS developed from theses focus groups with another qualitative approach (Luquiens, Whalley et al. 2014), except for memory loss and cognitive impairment, which has been interestingly identified by the French patients as very close to loss of behavioral control. This understanding is supported by fundamental data linking impulsivity, deficits in cognitive control and aggressive reactions (Gan, Guevara et al. 2014; Dambacher, Sack et al. 2015). This study supports the first analysis of these focus groups (Luquiens, Whalley et al. 2014) that proposed the inclusion of control domain as part of the core impact on quality of life of alcohol consumption.

The different recruitment settings between the French and the English patients could explain the different sources of help reported by the two groups of patients. French patients have been included in addiction specialized centers, and were therefore, no matter their AUD status, invested and motivated to change their alcohol consumption. They spontaneously referred to professional sources of help and to medical care. On the contrary, English patients were recruited in other departments but addiction department, and were not asking for help regarding their alcohol consumption. Some of them recovered thanks to mutual

support groups such as the Alcoholic Anonymous, or the Intuitive Recovery, which are available in the environment of the Liverpool hospital. This could explain that some referred to mutual support groups, and others referred preferably to close relatives, and especially family members, that are the more easily available potential supporting people among non-help-seeking people. More than a cultural difference, the discrepancies in the description of sources of help could be due to the help- or non-help-seeking status of the patients. However, mutual support groups are much more available in UK than in France, even if French guidelines highlights the potential benefits of attending these groups (SFA, ANPAA et al. 2015). The separate notification of alcohol withdrawal symptoms and physical impairment could also be due to this difference of characteristics in help-seeking status. French patients refer less to withdrawal symptoms maybe because there are handled with some medications, whereas English patients have to deal with them on their own. However it is interesting to note that physical impairment is not the core of the impact on quality of life, described in another class. It is a therefore critical issue to use scales giving a large place to physical impairment in assessing HRQOL among patients with alcohol use disorder, as it has been hypothesized in previous research (Luquiens, Reynaud et al. 2012). Moreover, the remitted non-help seeking English patients and the non-remitted help-seeking French patients are those who reported the largest part of the impact of alcohol consumption on quality of life (vs respectively the non-remitted English and the remitted French patients). One explanation of this difference could be that treatment process includes, by its motivational component, the identification of domains of life impacted by alcohol consumption. The motivational aspect of assessing quality of life had previously been noted (Ugochukwu, Bagot et al. 2013), and our data support this hypothesis. The completion of AQoLS, the only HRQOL scale specific to alcohol use disorder and derived from the focus groups reported in this study, could then serve as a motivational tool helping the detailed identification of domains of life impacted by alcohol consumption, and explored by items that are identified as matching patients' concerns. It could allow drawing a detailed picture of the personal situation of patients and thus guide the care in a patient-centered approach.

Limits

Participants had probably a good therapeutic alliance, since they were asked to attend a 2 hours group with no monetary compensation. This could have constituted a recruitment bias. Moreover, no patient with alcohol abuse was included. Therefore these findings document quality of life impact of the more severe end of the alcohol use disorder spectrum, which was the initial population of interest. These data could be interestingly complemented by data among alcohol abusers or frequent binge drinkers not fulfilling the criteria for alcohol dependence.

The number of EUCs classified was correct in both corpuses and enough to enable the analyses, but remained limited. The French corpus was less rich than the English corpus, but the latter is composed of more "noise", which is content not strictly related to quality of life, classified in class 5. Some of the so-called "noise" was the report of a difficult personal history from one patient. It probably comes from a less directive way to lead the groups in UK, to the personality of the included patients or because the included patients were more used to mutual support groups, and could then be more used to share their personal history, regardless the initial purpose of the session.

The cross-cultural dimension of the content is limited to two European countries and cannot be generalized without caution to other countries. As some of the findings seem to be related to the different characteristics of the investigator settings, these data should be reproduced cross-culturally within similar settings to determine the role of help-seeking status in the ability in spontaneously identifying the impacted-by-alcohol domains of life among patients with alcohol dependence.

CONCLUSION

Despite differences in the drinking habits, the domains of life impacted by alcohol identified by the patients were similar across the two countries. Patients with current or remitted

alcohol dependence gave particular salience on constraint of alcohol consumption, the self-esteem impairment, loss of behavioral control and cognitive difficulties. These domains newly understood as part of HRQOL among alcohol dependent patients are confirmed to be non-country-specific and non-impacted by specific drinking habits. Moreover, the help-seeking status could impact the ability in spontaneously identifying domains of life impacted by alcohol. Patients could benefit from an active help to identify these domains as part as the treatment motivational process.

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TABLES AND FIGURES

Table 1: Characteristics of the Focus Groups Patient Sample

Characteristic	UK (n = 17)	France (n = 21)
Age (years)		
Median (IQR)	42 (38-52)	48 (42-50)
Range	23-65	31-69
Sex [n (%)]		
Male	12 (70.6)	14 (66.7)
Female	5 (29.4)	7 (33.3)
Relationship status [n (%)]		
Married or living as	3 (17.6)	10 (47.6)
Not married or living as	14 (82.4)	11 (52.4)
Employment status [n (%)]		
Working	5 (29.4)	11 (52.4)
Not working	12 (70.6)	10 (47.6)
DSM-IV diagnosis [n (%)] ^a		
Dependence	17 (100)	21 (100)
Abuse	0 (0)	0 (0)
MINI dependence score ^b		
Median (IQR)	6 (5-7)	5 (4-6)
Range	4/7-7/7	3/7-7/7
AUD status [n (%)]		
Current	8 (47.1)	12 (57.1)
Remitted	9 (52.9)	9 (42.9)
Number of drinks on a typical occasion [n (%)]		
3-4	0 (0)	2 (10)
5-6	3 (18)	6 (29)
>6	12 (70)	13 (62)
Frequency of having 6 or more drinks on one occasion over last year [n (%)]		
Weekly	1 (6)	7 (33)
Daily or almost daily	13 (76)	14 (67)
Time since first contact with health services (years) (mean, sd)	4.5 (5.9)	5.7 (5.8)

AUD = alcohol use disorder; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; MINI = Mini-International Neuropsychiatric Interview; IQR = interquartile range.

^a DSM-IV dependence and abuse criteria assessed by the Mini-International Neuropsychiatric Interview 6.0 (14). Patients received a diagnosis of alcohol dependence if they met a minimum of three out of seven dependence criteria. If the criteria for dependence were not met, the patient was assessed according to four abuse criteria; a minimum score of 2 was required for a diagnosis of abuse.

^b MINI dependence score is the number of dependence criteria met; scores can range from 0 to 7, with a minimum of 3 required for a diagnosis of alcohol dependence.

Table 2: Examples of Elementary Units of Context (EUCs) associated to class 1 ($\chi^2 \geq 3.84$) in the English corpus

<i>EUC n°</i>	Quotation
1258	“It makes us selfish. It turns us from being nice, affable people and to me personally into a violent nasty verbally abusive, robbing, do anything, anything, hurt anyone who gets in my way, tries to take the drink off me.”
1668	“I lost my flat yeah. Lost everything. I was living in an abstinence house where you are not allowed to drink. It was a supported house. Not allowed to drink, not allowed to do any kind of illegal substances. And this is where me and my partner were staying and ended up drinking.”
0796	“So I’ve started to notice that myself, picked up on it. But the final straw was when I actually self-harmed under alcohol and police were called and I was arrested and everything else, because there was a knife involved.”
1262	“My mum says you’re not my son when you drink. You re a totally different person, your eyes change, your face changes, your mannerisms change. Everything about you gets tense.”
1582	“But that, it ruined my life because I used to love going out but while you re drinking, it totally bollocks up my sex life.”
0032	“And I know that they are elevated again and it just looks to remain that way. So literally, health was never an issue. Although I was a mess, I was very emotional, couldn’t function properly, complete and utter apathy with friends, with family, with work colleagues, with my job, I just wasn’t bothered.”
0667	“Well, because of your timetabling your life around it, it’s difficult to make plans and follow it through today so far, we’re on a cycle, do you know what I mean?”

Figure 1: The dendrogram (from top-down hierarchical classification analysis) and the major associated words ($\chi^2 \geq 4$) on the French corpus. (Form (Khi-2, frequency))

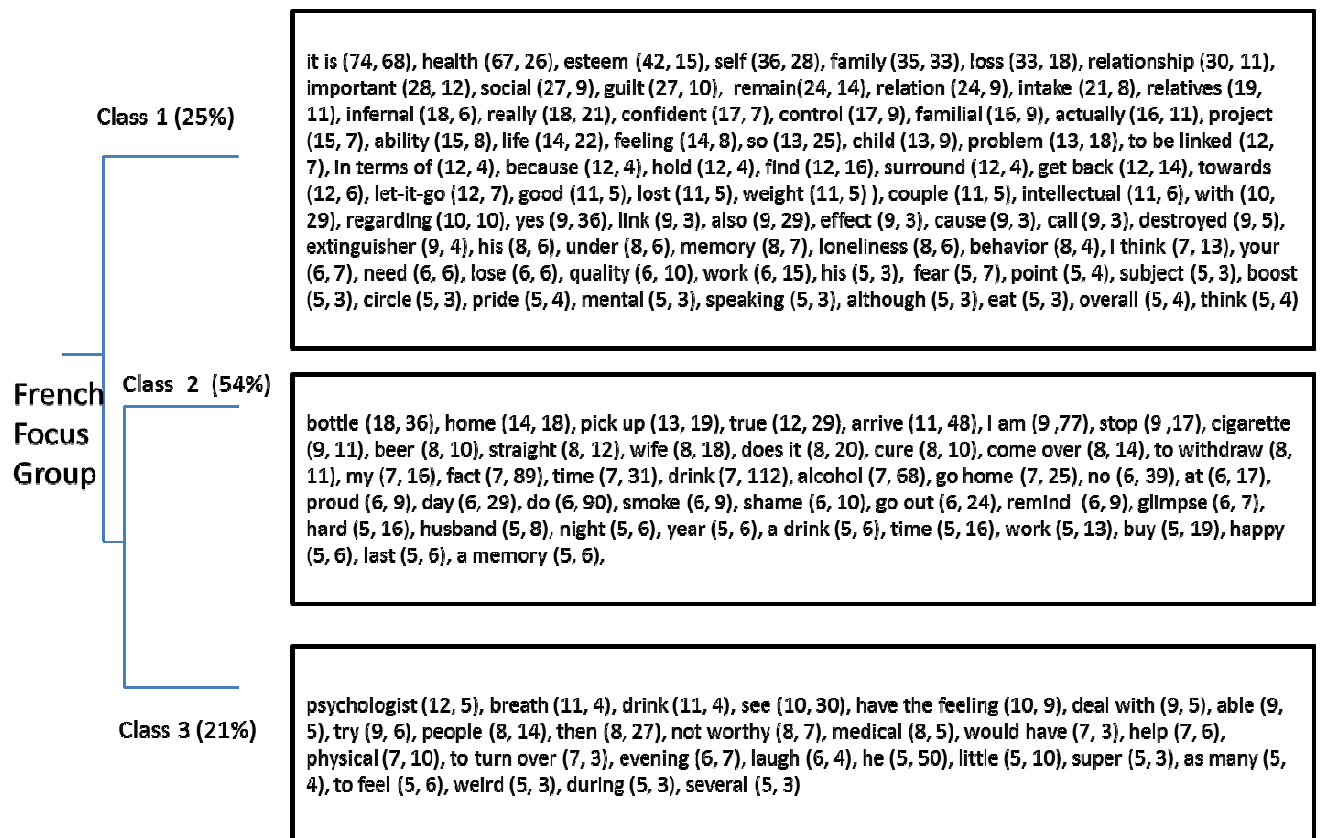
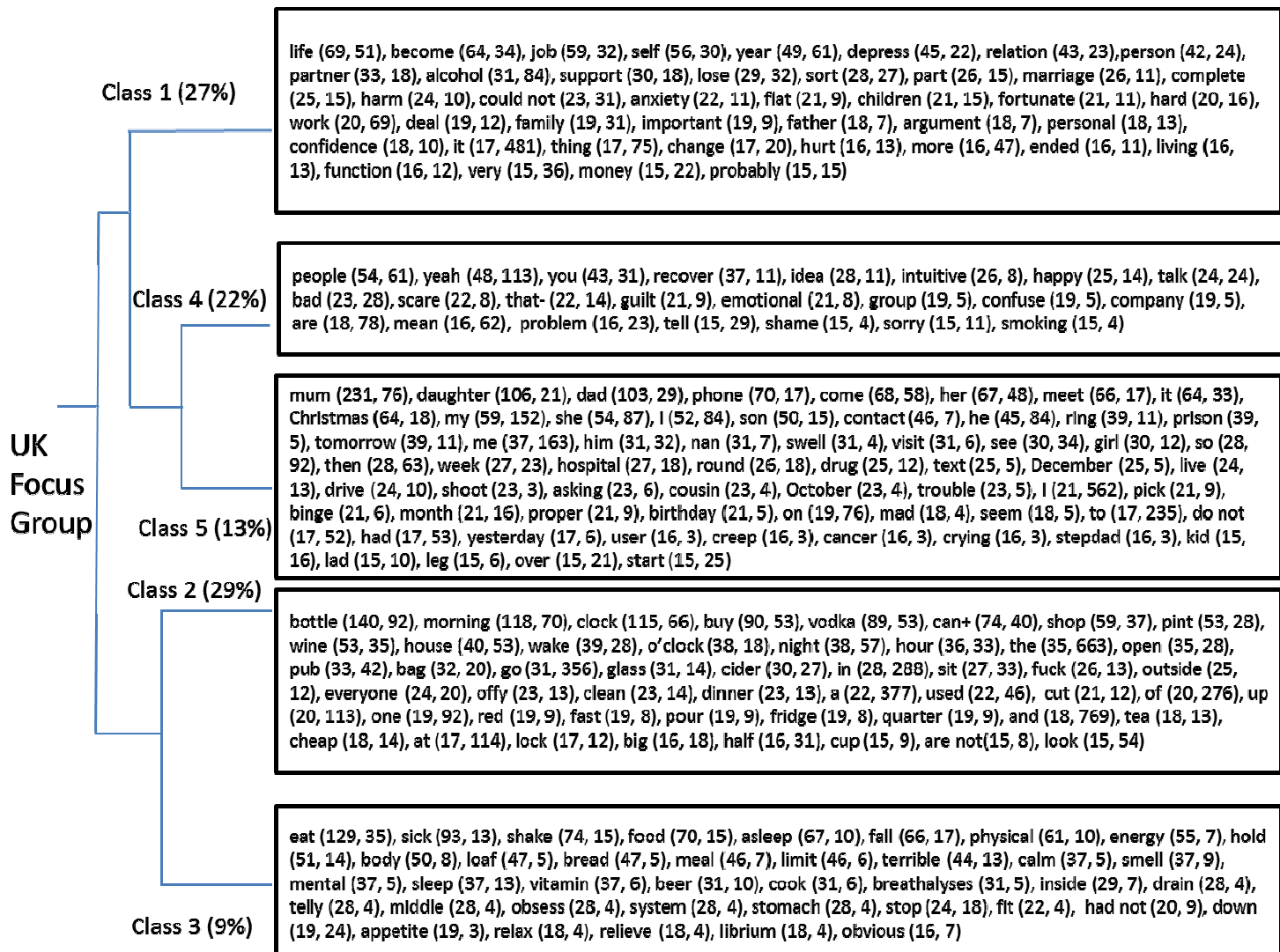
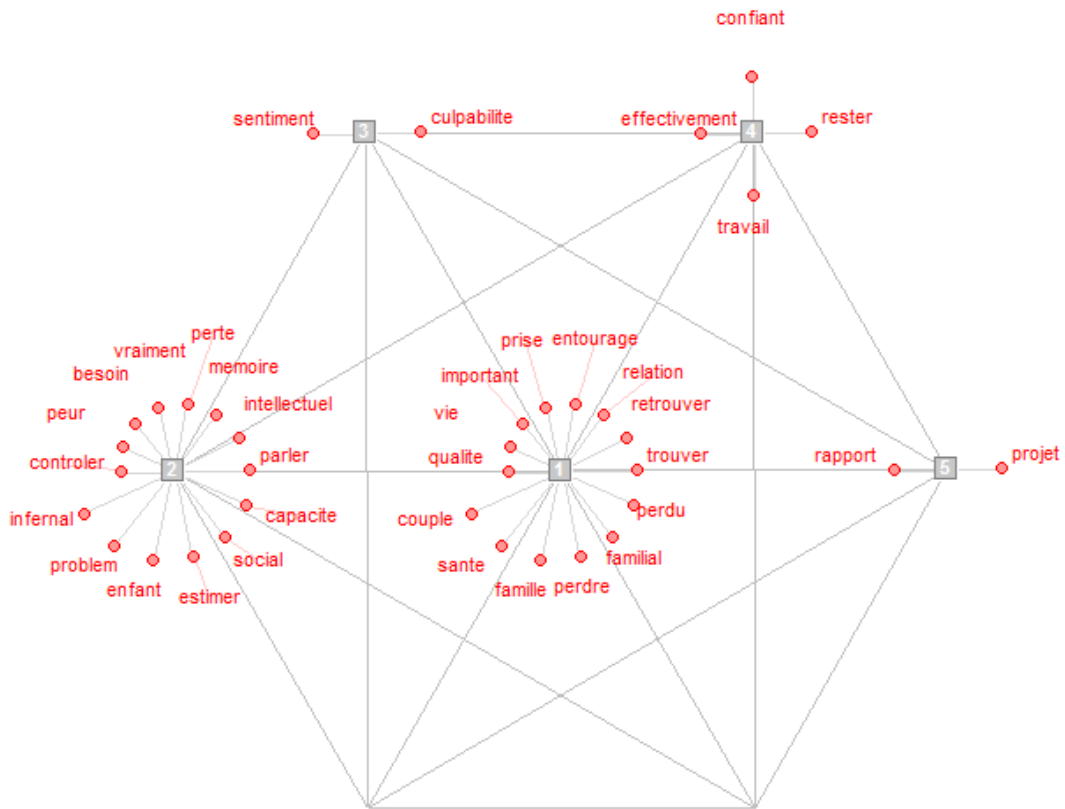


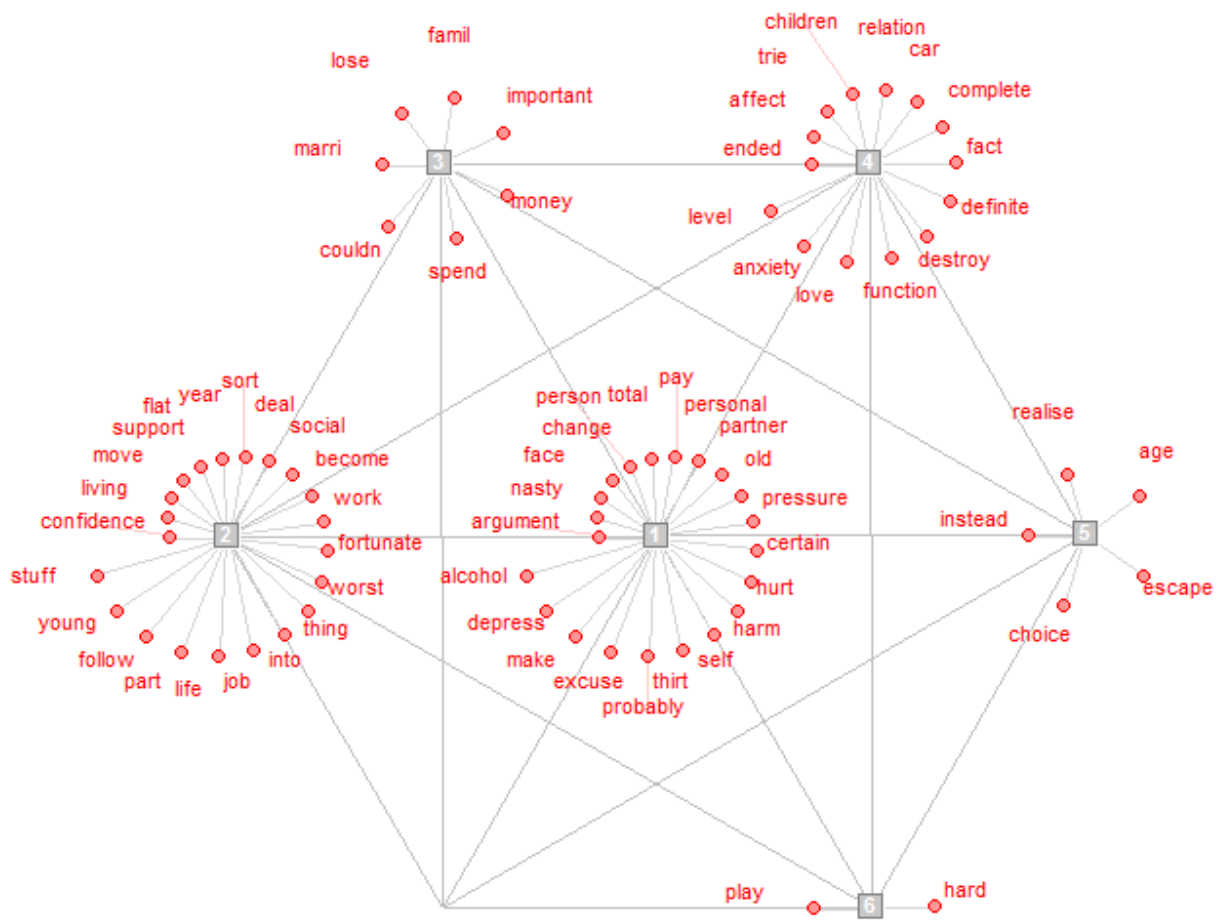
Figure 2: The dendrogram (from top-down hierarchical classification analysis) and the major associated words ($\chi^2 \geq 15$) on the English corpus). (Form (Khi-2, frequency))



Supplementary online only figure 1: cluster analysis of class 1 (French corpus) (cosines similarity)



Supplementary online only figure 2: Cluster analysis of class 1 (English corpus) (cosines similarity)



Validation transversale de l'échelle AQoLS (Luquiens et al. en révision)

L'article «Luquiens, A., D. Whalley, et al. (in Rev). "Validation of a new patient reported outcome instrument of health-related quality of life specific to patients with alcohol use disorder: the Alcohol Quality Of Life Scale (AQoLS)." Quality of life research» soumis en anglais est ici synthétisé en français, puis inséré dans sa version complète en anglais.

Après avoir développé l'échelle AQoLS, il s'agit de déterminer ses propriétés psychométriques et sa validité de structure et de construit. L'analyse présentée ici constitue le premier rapport de validation transversale dans une population de patients présentant un trouble d'usage d'alcool en France.

Méthodes

Population

Cette étude est une partie d'une étude plus large prospective dans 8 pays européens dont la France (Rehm, Allamani et al. 2015). Les patients étaient recrutés en milieu spécialisé addictologique. En France, un échantillon de 285 patients présentant un trouble d'usage d'alcool et traités dans un des 6 centres investigateurs ont été inclus dans l'étude.

Mesures

Des caractéristiques sociodémographiques et l'Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) ont été recueillis.

L'échelle AQoLS a été complétée par tous les patients, ainsi que deux autres échelles de QVLS génériques présentées précédemment, l'EQ-5D et la SF-36 (les deux échelles les plus

utilisées jusqu'à présent) pour les patients de trois des centres, ces deux échelles ayant été ajoutées au protocole après le début des inclusions.

Analyses statistiques

Nous avons reporté selon les recommandations du groupe COSMIN les éléments suivants: validité de structure, consistance interne, validité de construit et test des hypothèses de construit.

Le score total de l'échelle était obtenu en sommant les items. Chaque item était coté de 0 (pas d'impact) à 3 (extrêmement impacté).

Validité de structure:

AQoLS est basée sur un modèle réflectif. La validité de structure a été analysée avec le score total et donc avec les données des patients pour lesquels il n'y avait pas d'item manquant. Une analyse factorielle exploratoire a été réalisée pour explorer la structure dimensionnelle de AQoLS. Le nombre de facteur optimaux a été identifié à partir d'une analyse en composante principale par l'observation graphique du point d'inflexion du scree plot selon la méthode de Catell. La présence sur le scree plot d'une première dimension substantielle était recherchée pour soutenir la pertinence du calcul d'un score total en sommant les items.

Validité de construit et test d'hypothèses

Pour évaluer la validité de construit, les corrélations par le test de Spearman entre le score total de AQoLS et les dimensions de l'EQ-5D, de la SF-36 et de ses scores résumés ont été calculées. Nous avons posé l'hypothèse d'une congruence dans la direction des corrélations entre les échelles, et de corrélations modérées avec les scores sauf avec les scores relatifs à des dimensions purement physiques où nous avons l'hypothèse de corrélations faibles.

Consistance interne

Nous avons évalué le coefficient alpha de Cronbach pour le score total et les scores des dimensions. En effet, même si nous nous appuyons sur un modèle réflectif, nous pensons que les scores des dimensions peuvent servir à étudier l'efficacité d'interventions ciblées sur certaines composantes de la qualité de vie.

Résultats

Population

Un total de 285 patients traités pour un trouble d'usage d'alcool en milieu spécialisé a été inclus. Il s'agissait pour 65% d'hommes, l'âge moyen était 48 ans, le score AUDIT-C moyen de 6 et tous les patients étaient considérés comme alcoolodépendants. 1/3 des patients était sans activité professionnelle.

Distribution du score AQoLS

Le score total a pu être calculé pour 236 des 285 patients. Le taux de données manquantes variait de 2 à 4% selon les items, et il n'a été observé ni d'effet plancher ni d'effet plafond.

Validité structurelle

Le scree plot a montré une dimension majoritaire autorisant le calcul d'un score total. Sept dimensions ont été identifiées graphiquement avant le point d'inflexion du scree plot.

Une analyse factorielle à 7 facteurs a été réalisée avec la rotation Varimax. 21 des 34 items ont obtenu la charge la plus lourde sur leur dimension hypothétique pensée a priori. Plusieurs items ont présenté des charges proches (différence maximales 0.11) sur plusieurs dimensions, nous avons choisi de les attribuer à leur dimension hypothétique. Cinq items présentaient des charges faibles < 0.5 pour toutes les dimensions. Nous avons choisi de les conserver tout de même car aucun de ces facteurs ne présentant de problème de qualité, notamment le taux de données manquantes était bas et similaire à celui des autres items

($\leq 4\%$), on ne retrouvait pas d'effet plafond ni plancher pour ces cinq items et ils ne semblaient pas redondants;

Au final, deux dimensions hypothétiques ont été pleinement confirmées avec tous les items rattachés hypothétiquement à ces dimensions attribués ayant la charge la plus élevée pour celle-ci lors de l'analyse factorielle: le contrôle et le sommeil. Certains items de cinq dimensions ("émotions négatives", "activités", "relations interpersonnelles", "prendre soin de soi") ont été redistribués sur des dimensions différentes "(activités", "relations interpersonnelles", "conditions de vie"). En effet, la dimension "prendre soin de soi" n'a pas été observée, mais une septième dimension a émergé de l'analyse, "l'estime de soi", regroupant les items 12 "confiance", 14 "amis", 19 "honte", item 20 "mépris" et 21 "gâcher sa vie".

Validité de construit:

Comme expliqué précédemment, les échelles EQ-5D et SF-36 n'ont été complétées que par les 60 patients restant à inclure au moment où ces échelles ont été amendées au protocole. Le taux de données manquantes pour ces échelles était $\leq 7\%$ pour tous les items sauf cinq des items de la SF-36 (taux de 8 à 11%). La corrélation des dimensions de la SF-36 avec AQoLS était moyenne, conformément à nos hypothèses, sauf pour le score de fonctionnement social et d'état de santé général. Comme attendu également, le score de composante mentale était corrélé fortement à AQoLS ($r=0.7$, $n=35$) et le score de composante physique était faiblement corrélé à AQoLS ($r=0.1$, $n=35$). En ce qui concerne l'EQ-5D, les scores d'activité, et anxiété étaient modérément corrélés à AQoLS, mais le score de mobilité était aussi modérément corrélé à AQoLS, alors qu'on l'attendait plus faible. Comme attendu, les scores de douleur et d'autonomie étaient faiblement corrélés à AQoLS ($r \leq 2$). La direction des corrélations montrait une congruence entre AQoLS et les autres échelles, sauf pour les scores de santé générale de la SF-36 et de l'EQ-5D, ce qui pourrait

évoquer une inversion du score chez les malades les plus sévères avec la SF-36 et l'EQ-5D, connues pour être sensibles à ce phénomène.

Consistance interne

Le coefficient de Cronbach du score total était de 0.96, et celui des dimensions issues de l'analyse factorielle de 0.8 à 0.9.

Discussion

La validation transversale de AQoLS dans une population de patients alcoolodépendants a montré la pertinence du calcul d'un score total et une structure à 7 dimensions différant légèrement des dimensions pensées hypothétiquement. Les dimensions observées étaient "activités", "relations interpersonnelles", "émotions négatives", "sommeil", "contrôle" et "estime de soi". Les 34 items ont été conservés car de bonne qualité et pertinents cliniquement sans redondance évidente.

Deux dimensions n'étaient pas jusqu'à présent considérés comme faisant partie de la qualité de vie liée à la santé dans le trouble d'usage d'alcool: le contrôle et l'estime de soi. Le contrôle était une des dimensions pensées hypothétiquement lors du développement de l'échelle. Le contrôle semble particulièrement pertinent cliniquement puisqu'il constitue le symptôme cœur de l'addiction sous la forme de la perte de contrôle aussi bien cliniquement que d'un point de vue neuropsychologique (contrôle inhibiteur) et neural (rôle des régions préfrontales en particulier) (Muraven and Shmueli 2006; Piazza and Deroche-Gamonet 2013; Volkow and Baler 2014; Wilcox, Dekonenko et al. 2014) . L'échelle AQoLS permet ainsi une réconciliation entre le point de vue d'expert et le point de vue centré sur le patient, en explorant en tant que plainte du patient ce qui était jusque-là souvent considéré comme un facteur pronostic ou de risque, ou bien comme un symptôme évaluable par un tiers. L'estime de soi n'était pas explorée dans les instruments mesurant la QVLS chez l'adulte. Pourtant, la qualité de vie est connue pour être faible chez les alcoolodépendants (Tikka, Ram et al. 2014), et a été décrite comme associée à la qualité de vie globale (Hibbert and

Best 2011) et proposée comme faisant partie de la qualité de vie globale dans une échelle, la Life situation survey (Chubon 1999 revised), validée secondairement chez l'alcoolodépendant (Foster, Marshall et al. 2000).

La corrélation modérée avec les autres échelles de qualité de vie montre que AQoLS ne se comporte pas comme une échelle redondante aux existantes. Le libellé des consignes interrogeant directement les patients sur le rôle de l'alcool pourrait expliquer cette corrélation modérée alors même que certaines dimensions comme les activités et les relations interpersonnelles sont communes entre AQoLS et les échelles SF-36 et EQ-5D. Cela pourrait aider les patients à faire le lien sur le rôle de l'alcool sur leur qualité de vie, alors qu'il pourraient répondre négativement à des consignes concernant leur "santé", notamment par un processus d'auto-stigmatisation situant leur problème d'alcool en marge de leur état de santé. Les corrélations faibles avec les scores physiques viennent confirmer notre hypothèse de manque de pertinence de ces items des échelles génériques en ce qui concerne le trouble d'usage d'alcool.

La limite majeure de cette analyse est son caractère transversal. Il reste nécessaire de documenter le comportement de l'échelle dans le temps et sa sensibilité au changement.

Validation of a new patient reported outcome instrument of health-related quality of life specific to patients with alcohol use disorder: the Alcohol Quality Of Life Scale (AQoLS) [in 2nd Revision in Quality of life Research]

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Running head: Validation of the AQOLS

Keywords: quality of life; alcohol use disorder; validation; psychometrics; control; self-esteem

ABSTRACT

Purpose

The Alcohol Quality of Life Scale (AQoLS) is a new patient reported outcome 34-items questionnaire measuring health-related quality of life (HRQOL), specific to patients with an alcohol use disorder, developed from the patients' perspective. This is the first report establishing evidence in support of measurement reliability and validity of the AQoLS.

Methods

285 randomly selected patients receiving interventions for alcohol use disorder in addiction specialised care settings in France were included in the study (response rate 80.1%). Exploratory factor analysis was conducted to evaluate the hypothesized-during-development-stage dimensional structure of the AQoLS. Internal consistency of the total score and the dimensions subscores were assessed through Cronbach's alpha coefficients. Construct validity was tested through correlations with the Short-Form 36 Health Survey (SF-36) and EuroQol 5 dimensions (EQ-5D).

Results

Exploratory analysis indicated 7 observed dimensions which differed slightly from the 7 dimensions defined *a priori* in the framework hypothesised during the scale development: activities, relationships, living conditions, negative emotions, self-esteem, control, and sleep. A major common factor allows the summing of the 34 items to obtain a total score. All the 34 items were acceptable. Cronbach's alpha for the AQoLS total score was 0.96 and ranged from 0.8 to 0.9 for the dimensions subscores. AQoLS was congruently and significantly correlated with most subscores of the SF-36, including the mental subscore, and the EQ-5D.

Conclusion

This study provides evidence of the measure's psychometric properties in terms of construct validity and internal consistency. The "control" and "self-esteem" dimensions are of particular interest as these concepts are not captured in existing HRQOL. Further longitudinal validation of the scale is necessary to assess sensitivity to change.

INTRODUCTION

Alcohol use disorders (AUD) have the widest treatment gap (78.1%) amongst psychiatric disorders worldwide (Kohn, Saxena et al. 2004). This could be partially explained by the fear to be proposed an abstinence-oriented treatment (SAMHSA 2012). These findings contributed to revisit the acceptability of strategies relying on reduction of alcohol consumption, supported by the recent modelling of harm reduction linked to reduction of alcohol consumption (EMA 2010; Rehm and Roerecke 2013). This context, along with the recent first European approval of a pharmaceutical drug to reduce alcohol consumption in alcohol dependent patients (EMA 2010; EMA-CHMP 2012; EuropeanMedicinesAgency 2013), highlights the need for nondrinking outcomes that could assess the efficacy of both abstinent and non-abstinent targeted interventions, and allow comparison between them.

Moreover, these evolutions can be considered as part of the more global development of patient-centred approaches, considering the drinking goal as only a surrogate endpoint of the patient global state improvement, that could be preferably measured by nondrinking outcomes (Luquiens and Aubin 2014). Even if alcohol consumption measures are adopted, its assessment can be difficult, with variations in reporting of alcohol consumed leading to different interpretations, especially when categorical variables are used, and when the goal of treatment is not abstinence (Sobell, Sobell et al. 2003). Categorical use could report with difficulty the non-linear change in drinking patterns. The non-linear change in drinking pattern has been recently taken into account by the Food and drug administration recommending a grace period when using categorical variables (FDA 2015). The use of continuous rather than categorical measures of alcohol consumption could increase the precision of the measurement, and thus the likelihood of finding true and relevant changes, even if they are not consensual (Robinson, Sobell et al. 2014). A recent review of alcohol outcome studies noted these difficulties, reporting that almost a quarter of reviewed studies failed to quantitatively assess alcohol use, the primary dependent variable, making it difficult or

impossible to evaluate substance use changes pre- and post-intervention (Robinson, Sobell et al. 2014).

Recently, several nondrinking qualitative concepts have emerged to measure patients' clinical states and outcomes: negatively related consequences, craving, and health-related quality of life (HRQOL). The concept of negative alcohol-related consequences has the disadvantage of coming mostly from the expert's point of view (Miller and Longabaugh 1995). Craving has shown complexity in its assessment because of its moving nature, and conceptual and practical issues regarding its measurement are still debated (Tiffany, Carter et al. 2000).

Health-related quality of life (HRQOL) is a nondrinking outcome consensually recognised in the AUD field as well as in evidence-based medicine as a whole (Donovan, Mattson et al. 2005; Drummond, Sculpher et al. 2005; Zubarán and Foresti 2009). HRQOL could be particularly valuable to assess the benefit of treatment, especially in non-abstinent targeted interventions (Raistrick, Heather et al. 2006). HRQOL reflects patients' feelings and functioning and the impact of their health condition beyond simple symptom assessment (Leplege 2011). Classically, HRQOL involves four domains: (1) physical state, including autonomy and physical abilities; (2) physical well-being, including pain and physical symptoms; (3) psychological state, including anxiety and depression; and (4) social relationships including the domains of family, friends and work (Leplege 2011). However, most generic scales, such as the SF-36 and the EQ-5D, have not been developed from the patients' but from the experts' perspective; most of them have been developed primarily for use among patients with somatic diseases such as cardiovascular disorders or cancer, who experience different symptoms from those experienced in AUD (EuroQolGroup 1990; McHorney, Ware et al. 1993). Moreover, as generic instruments are intended for use across a range of diseases, they are less able to capture the specific manifestations of a given disease, particularly complex disorders such as AUD. For example, they largely explore physical areas, such as self-reliance and pain, which do not seem the most relevant ones in

AUD (Luquiens, Reynaud et al. 2012). Although HRQOL is increasingly assessed in clinical trials in AUD, some generic scales could fail in exploring some specific relevant information in these patients (Luquiens, Reynaud et al. 2012). For example, a systematic review of quality of life instrument used in clinical trials in alcohol dependence has shown that generic instruments often fail to show a difference between treatment groups, even where the efficacy of the experimental intervention on a drinking outcome or other outcomes has been demonstrated (Luquiens, Reynaud et al. 2012). Similarly, social costs of AUD could be underestimated (Jeanrenaud, Priez et al. 2003), in part due to the lack of relevant specific scales assessing important aspects of quality of life in this disorder. Until recently, no quality of life instrument had been developed specifically for patients with AUD, leaving some potentially relevant areas unexplored.

In order to respond to these methodological, clinical and epidemiological issues, we developed the first patient reported outcome (PRO) measure of HRQOL, specific to patients with AUDs, the Alcohol Quality of Life Scale (AQoLS) (Luquiens, Falissard et al. 2012). The AQoLS has been developed from the patients' perspective, using focus groups and individual interviews with subjects with current or remitted AUD in France and the United Kingdom. The development followed industry-recognised standards for patient reported outcome instruments used in clinical trials (FDA 2009), including an iterative process for deriving the underlying conceptual framework and extensive patient input throughout the development process to ensure content validity. This methodology ensures that the AQoLS reflects patients' concerns and can be used to explore the global impact of AUD on patients' HRQOL. The methodology employed for the development of the scale development is described in detail elsewhere (Luquiens, Whalley et al. 2014). Briefly, an initial, conceptual framework for the AQoLS was developed from a previous systematic review of HRQOL instruments conducted by Luquiens et al. [10]. A discussion guide for the running of the focus groups relied on this framework to help exploration of potential HRQOL concepts in the concept elicitation stage. To reduce country-specific characteristic bias of the new measure,

all developmental stages of the AQoLS were conducted simultaneously in the United Kingdom (UK) and France. The content was developed from the qualitative analysis of focus groups in the UK and France involving 38 English and French patients with current or remitted AUD of varying levels of severity. Patients were asked to share the impact that alcohol had had or was having on their life. The sessions were transcribed and a thematic analysis was used to identify key areas of impact of AUD, and draft items were developed to capture these issues. The draft items of the AQoLS underwent expert review to ensure clinical and cross-cultural applicability. AQoLS has previously shown good face and content validity through two iterative rounds of cognitive debriefing interviews conducted with 31 patients with current or remitted AUD in both countries (Luquiens, Whalley et al. 2014).

This is the first report establishing evidence in support of measurement reliability and validity of the AQoLS.

METHODS

Setting and patient sample

This validation study is part of a larger survey taking place in 8 European countries, including France (Rehm, Allamani et al. 2015; Rehm, Allamani et al. 2015). The study is a personal interview-based investigation among patients with AUD aged 18-64 years to gain an understanding of the medical needs in this population. The study presented in this article is a nested-study aiming to validate the French version of the AQoLS.

Patients were recruited in French addiction specialised care settings. 6 centres were randomly selected from a register of 161 addiction specialised care sites across the country. The random sampling method was chosen to enhance the representativeness of our sample in order to reflect the treatment system for AUD in France. 285 out-patients currently treated for an AUD were included in the study. All adult subjects aged 18-64 years in the specialised care settings who had AUD (either current or remitted) and who were undergoing treatment for their disorder were eligible to be part of the study. The study was proposed systematically

to each patient attending a medical appointment in the investigation site on a preselected day and treated for AUD. The included patients were then proposed an additional appointment to complete the study assessments. Patients signed a written and informed consent forms after having being explained the purpose of the study. The study met the French requirements for observational studies and was approved by the *Comité Consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé* (CCTIRS) on 04/24/15, Number 13.222.

Assessments

Patient demographics and disease state

Sociodemographic characteristics were collected from patients, including age, gender and employment. Patients also completed the AUDs Identification Test Consumption (AUDIT-C), a brief screening questionnaire which reliably identifies patients who have current AUD (Bush, Kivlahan et al. 1998) (range 0 to 12). A score ≥ 4 (men) or 3 (women) is considered as a proxy for AUD (Bradley, Bush et al. 2003).

AQoLS

Patients included in the validation study self-completed the AQoLS on a single occasion in the health care setting, during a dedicated interview. The AQoLS is a self-completed questionnaire composed of 34 items and 7 *a priori* dimensions hypothesised during the development stage: activities (items 1 to 6), relationships (items 7 to 14), living conditions (items 15 to 18), negative emotions (items 19 to 23), looking after self (items 24 to 27), control (items 28 to 32), and sleep (items 33 to 34). A 4-point Likert-type response scale (“not at all” (0), “a little” (1), “quite a lot” (2) and “very much” (3)) was selected to balance responder burden and the potential measurement sensitivity of the items. The recall period is 4 weeks.

Additional HRQOL scales

Additional HRQOL scales were amended to the clinical research form after the beginning of the inclusion period. Inclusions were ended up in 3 of the 6 investigation centres at the amendment time. All 60 remaining patients to be included in the 3 other centres systematically self-completed the additional HRQOL scales (SF-36 and EQ-5D) in addition to AQLS, during the same dedicated interview as mentioned above. Characteristics of this sub-sample of patients were described.

The Short-Form 36 Health Survey (SF-36) was derived from the Medical Outcome Study (Ware and Sherbourne 1992), an observational study that began in 1986 among subjects with cardiac impairment. It is a 36-item questionnaire that includes eight dimensions: physical functioning, physical role limitation, emotional role limitation, bodily pain, mental health, social functioning, vitality and general health perception. It also includes two component summaries: mental (MCS) and physical (PCS). It was validated in a French version among 147 alcohol dependent patients. In this population, test–retest intraclass coefficients for a 0–10 days interval were in the range 0.65–0.79, whereas the Cronbach alpha coefficient indicated good internal consistency (range 0.70–0.89) (Daeppen, Krieg et al. 1998).

The EuroQol 5 dimensions (EQ-5D) is a generic, preference-based instrument for describing and assessing HRQOL in terms of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension comprises three levels, resulting in a total of 243 unique health states. Among 52 alcohol dependent patients, it showed only trivial to medium responsiveness at 18 months (Gunther, Roick et al. 2007), and probably requires large patient samples in order to detect meaningful clinical differences. The EQ-5D has not been explicitly tested for measurement properties in individuals with AUD in any language. The standardized extended version of EQ-5D was designed for the collection of health state values using a VAS rating scale - a vertical 20 cm visual analogue scale with the

end points labelled best imaginable health state at the top and worst imaginable health state at the bottom having numeric values of 100 and 0 respectively.

Statistical analysis

Descriptive analysis of the population demographics and disease severity was performed.

As content and face validities were documented in a previous publication, we report here, according to the COSMIN checklist with a 4-point scale (Mokkink, Terwee et al. 2012): internal consistency, structural validity and construct validity and hypothesis testing.

The total score was obtained by summing all items, the theoretical range was therefore 0-102; method to assess the appropriateness of calculating a total score is described below. The AQoLS total score and domain scores were described in the study population. Distribution of responses per item was studied to assess acceptability and upper and lower limit effects of the scale.

Validity

Structural validity

Only patients who had completed all items of AQoLS were included in the structural validity analysis. There was no data imputation. AQoLS is based on a reflective model. Exploratory factor analysis was conducted to explore the dimensional structure of the AQoLS. The optimal number of factors was identified from a preliminary principal component analysis, using Cattell's scree plot inspection for the point of inflexion (Cattell 1966). A scree plot is the plotting of the eigenvalues of the correlation matrix in decreasing order, with the components as the X axis and the corresponding eigenvalues as the Y-axis. A first substantial dimension on the plot would support graphically the appropriateness of calculating a total score summing all the items. A factor analysis with Varimax rotation was performed with the number of factors identified from the principal component analysis. Items were attributed to the dimension for which they had the highest loads; exceptions were: (1) when 2 loads were

close, the a priori dimension could be kept, or (2) when several loads were close, the item could be attributed to the more relevant dimension.

Item-dimension correlations were calculating, omitting the item from its dimension, in order to avoid artificially inflated correlation (Spearman test)(Streiner, Norman et al. 2014).

Construct validity and hypothesis testing

For assessment of construct validity, Spearman correlations between the AQoLS scores and EQ-5D dimension scores, EQ-5D health state score, and SF-36 dimension and summary scores were calculated. We hypothesized congruency in the direction of the association regarding the AQoLS total score and SF-36 ad EQ-5D scores (namely a negative association with SF-36 and a positive association with EQ-5D), a moderate correlation with the overall scores and low correlation with dimensions reporting exclusively physical areas, namely: physical functioning, physical role limitation, bodily pain, mental health subscores of SF-36 and physical component summary (PCS) of SF-36, and , i.e. mobility, self-care, pain/discomfort of EQ-5D.).

Internal consistency

We believe that a total score could be useful to assess interventions efficacy in alcohol use disorder, and that subscores could also inform more precisely on efficacy of targeted interventions on a particular domain, and could be particularly interesting in assessing targeted interventions. Therefore, internal consistency was assessed for each dimension of the AQoLS and for the total score using Cronbach's coefficient alpha.

All the analyses were performed using R 3.0.3 software.

RESULTS

Patient sample

A total of 285 French patients treated for an AUD in a specialised care setting were included in this analysis. This sample size fits with the current guidelines regarding validation of scales (Rouquette and Falissard 2011). Sixty percent of all specialized care facilities contacted via phone refused to be part in the study because they refrain from studies in general. Near 20% of patients refused to participate because lack of time and reluctance to attend an additional appointment for the study completion (figure 1). The sample was composed of 65% male patients. Mean age was 48 years. This demographic profile is close to the one usually observed in the selected settings. Mean AUDIT-C score was 6. All women and all men had an AUDIT-C score above 3 or 4 respectively, considered positive for the current year. Unemployment due to medical or other reasons was observed in 33% of the included patients. The subsample of patients who completed the other HRQOL scale had very similar characteristics: 65% male patients, mean age 50, mean AUDIT-C score was 6, all patients had an AUDIT-C score above 3 (female) or 4 (male), and unemployment rate was 30%.

AQoLS score distribution

An AQoLS total score could only be calculated in 236 of the 285 patients (82%) due to missing data. The missing data rate for each item varied from 2% to 4%. All items were, therefore, well accepted by patients. The total range of responses from 0 to 3 was used for each item of the AQoLS, indicating no lower or upper limit effect. The AQoLS total mean score was 45.3 (sd=22.1), with a range 0 to 90 (0 to 102 is the maximum possible score range) Score 0 was obtained for 4% of the completers (n=9), and score 102 was obtained for 0% of the completers (n=0) (figure 2).

Validity

Structural validity

The question of dimensionality of the construct is addressed in two different ways. These two steps are based on exploratory analysis. First, a scree plot is shown (figure 3). The preliminary principal component analysis indicated a substantive principal dimension accounting for 42% of the variance, thus indicating the appropriateness of a total AQoLS score summing the items. Seven dimensions were graphically identified before the point of inflexion, accounting for a total of 60% of the variance.

Table 1 presents the 7-factor solution from the factor analysis with Varimax rotation. 21 of the 34 items had the highest loading on their *a priori* dimension. . Several items presented loadings close in two dimensions; we chose to include them in the dimension which seemed more meaningful, even if the loading was lower in the corresponding dimension (differences in loading between the highest and the chosen dimension < 0.11). A minimum loading of 0.5 is usually taken to explore to dimensions of the construct (De Vet, Terwee et al. 2011). Five items presented low loadings < 0.5 on all dimensions including on their *a posteriori* dimension (range 0.26 to 0.47: 3- restricted in places; 7- cut myself off; 13- sex; 25- appearance; 19- shame). However, considering the original content of these items, that they do not overlap with the other items, their high clinical relevance, and that they are referring to areas that were particularly highlighted in the focus groups of patients that lead to the item generation, we chose to keep these 5 items in the AQoLS. Moreover, missing data rates for these items are similar to the other items (n=11, 9, 12, 9, 8, ≤4% for all five items).

-Two *a priori* dimensions have been fully confirmed: “control”, and sleep with all items having the highest loading on these factors.

-The loadings of some items differed from the *a priori* structure.

Specifically, four dimensions were partially confirmed. The “negative emotions” dimension grouped the 2 items related to worry. Three other items were *a posteriori* related to the “activities” dimension: item 15 - household-affairs, item 25 - appearance and item 26 - general-health. One was removed from “activities” to “relationships”; item1-everyday activities. Two items were *a posteriori* related to the “relationship” dimension: item 1 - everyday-activities and item 27 - risky-situations. Item 24 - appetite was *a posteriori* related to the “living conditions” dimension.

-Finally, the *a priori* dimension “looking after self” was not observed. Respective items were related to “living condition” (item 24-appetite), “activities” (items 25-appearance and item 26-general health), and “relationships” (item 27-risky situations).

A posteriori, a seventh dimension could be described and titled “self-esteem”, grouping the following items: item 12 - trust, item 14 - friends, item 19 - shame, item 20 - contempt and item 21 - wasting-my-life.

Construct validity

Table 2 shows the mean scores on the SF-36 and EQ-5D. As explained in the methods section, in both cases, the sample size is smaller due to the inclusion of the scales in the clinical research form after the beginning of the inclusions (n=60).

Missing data per item was $\leq 7\%$ for all SF-36 and EQ-5D items except for 5 of the 36 SF-36 items: 4.1, 5.1, 5.2, 9b and 11d (range of missing data 8 to 11%). Acceptability of these two scales was then lower than AQoLS acceptability. Correlations magnitude with dimensions of the SF-36 were moderated and ranged from 0.4 (emotional well-being, n=54) to 0.6 (energy/fatigue subscore, n=57), except for social-functioning and general health subscores which were very lowly correlated to AQoLS (respectively r magnitude=0.2 and 0.1, n=56 and 53). As expected, MCS was highly correlated with AQoLS total score (r=0.7, n=35), and

PCS correlation magnitude with AQoLS was very low ($r=0.1$, $n=35$). Regarding EQ-5D, mobility, activity and anxiety were moderately correlated to AQoLS total score (range 0.4 to 0.5, n respectively= 57, 57 and 59). As expected, correlations of AQoLS with pain and self-care (EQ-5D) were very low (magnitude ≤ 0.2) for, of As anticipated, all correlations' direction showed that an improvement in quality of life assessed with SF-36 or EQ-5D was correlated with an improvement of quality of life assessed by AQoLS, namely a decrease of the AQoLS score, except for SF-36 general health subscore and EQ-5D general health visual analogue scale, that were inversely correlated to AQoLS ; namely, an improvement of general health was correlated to a worsening of quality of life assessed with the AQoLS (respectively $r= 0.3$ $p< 0.05$, $n=53$ and $r=-0.4$, $p= 0.008$, $n=56$). Post hoc exploration for the possibility of a response shift in more severe patients by adjusting on audit C reduced the correlation to non-significance (linear regression, $p=0.51$).

Internal consistency

Cronbach's coefficient alpha for the AQoLS total score was 0.96, which shows excellent internal consistency. Cronbach's coefficients for the seven *a posteriori* dimensions ranged from 0.8 to 0.9.

Item-dimension correlations

Item –dimension correlations ranged 0.15 (item 8 –"negative emotions") to 0.83 (items 33 and 34 –"sleep"). Spearman correlation coefficients between items and dimensions of the AQoLS showed the largest correlation coefficient for each item with its *a posteriori* corresponding dimension, except for items 14 (relationships) and 24 (sleep).

DISCUSSION

This validation study of the AQoLS shows that a 7-dimension structure of the AQoLS was confirmed, with 34 acceptable items, in a population of French patients with current or

remitted AUD. Our data indicated 7 observed dimensions which differed slightly from the 7 dimensions defined *a priori*, of: “activities”, “relationships”, “living conditions”, “negative emotions”, “self-esteem”, “control” and “sleep”. Nearly two third of the items loaded on their *a priori* dimension, and the others were redistributed on the others *a posteriori* dimensions, leading in particular to the emergence of the ‘self-esteem’ dimension. Future use of this scale will clarify its behaviour and on the clinical relevance of dimensions’ subscores. The structure analysis with a major dimension allows the summing of the 34 items to obtain a total score. The AQoLS showed excellent internal consistency.

Methodological quality of reporting of internal consistency, structural validity and hypothesis testing including convergent validity was excellent according to the COSMIN checklist (Terwee, Mokkink et al. 2011).

Two unexplored dimensions

Two dimensions, control and self-esteem, are of particular interest because these aspects of patient HRQOL have been unexplored to date by the HRQOL instruments previously used in patients with AUD.

Control was an *a priori* dimension emerging from the content analysis of the focus groups during the AQoLS development. Control has high clinical relevance in addiction field: "loss of control "is a hallmark of addictions (Volkow, Fowler et al. 2010; Volkow and Baler 2014). Addiction has been described as a loss of control of drug intake, resulting from impaired prefrontal cortex function and long-term drug exposure (Piazza and Deroche-Gamonet 2013). Control has also been described as the core cognitive dysfunction in addictive behaviours (Muraven and Shmueli 2006; Noel, Brevers et al. 2013; Wilcox, Dekonenko et al. 2014). Although instruments assessing drinking-related control exist (Donovan and O'Leary 1978), control is not currently included in HRQOL instruments as a separate dimension. The advantage of the AQoLS is that it was developed using patients’ input, which allows the

inclusion of concepts identified by patients themselves as dimensions of HRQOL, and which have previously only been explored from the expert point of view. Control is no longer only a symptom described from the expert perspective, or a prognostic factor, but a difficulty reported by patients as having a significant impact on their quality of life, which they were willing to improve.

Similarly, instruments that assess self-esteem are available; the most commonly used being the Rosenberg Self Esteem Scale (Rosenberg 1965). Self-esteem has recently been shown to be lower in alcohol dependent patients than in healthy controls (Tikka, Ram et al. 2014). Moreover, self-esteem has been shown to be significantly associated with non-HR QOL, using the World Health Organisation Quality of Life-BREF measure, among remitted alcohol dependent patients (Hibbert and Best 2011). Self-esteem has previously been described as a dimension of a non-HRQOL instrument in the Life Situation Survey (Chubon 1999 revised), which was later validated in a population of alcohol dependent patients (Foster, Marshall et al. 2000). However, general non-HRQOL instruments, such as the Life Situation Survey, are reputed to be less robust than HRQOL ones, and their use as outcomes in clinical trials are not recommended. Self-esteem has also been previously included as a dimension in a HRQOL instrument designed for use among children, the German generic quality of life instrument for children (the KINDL) (Ravens-Sieberer and Bullinger 1998), but, to our knowledge, not in any HRQOL used among patients with AUD. Quotations from patients' from one of the focus groups consulted in the development of the AQOLS included: *"I got a quarter bottle of vodka and just necked it. Afterwards I felt guilty that I'd actually done it because I'd been actually trying to prove to myself and be strong for myself that I can do this. And when I had that relapse I felt really dirty on myself that I'd done it."* [United Kingdom-Focus Group 3_Remitted AUD]. This quotation illustrates how harsh patients were about themselves and how low their self-esteem was. Patients included these feelings as part of their impacted HRQOL, and noticed self-esteem to be sensitive to change over the course of the disease. Assessing self-esteem in HRQOL could be an informative outcome in patients

with AUD, reflecting patients' concerns. It thus seems relevant to include self-esteem as a distinct dimension of HRQOL in the AQoLS, even though not defined *a priori*.

These newly identified domains in measuring and monitoring HRQOL during assessment and treatment can add important value to patient recovery (Ugochukwu, Bagot et al. 2013). The patient-centred approach adopted throughout the development process of AQoLS could contribute to the recognition of the importance of the patient perspective in the treatment and outcome assessment in AUD, and help avoid a paternalistic style of health care, thereby reducing the residual stigma still impacting the health care system in this field (Wallhed Finn, Bakshi et al. 2014).

Construct validity

Support for the construct validity of the AQoLS was gained through congruent directions of AQoLS correlations with the majority of the dimensions of the SF-36 and EQ-5D. As expected, the correlations were mostly moderate in magnitude, low with scores referring to physical areas, and the highest with the MSC of the SF-36. This suggests that the AQoLS and traditional other HRQOL instruments are not superimposed on each other. This could be explained by the totally different methods in item generation between AQoLS, patient-centred, and the other scales, which have not benefitted from patients' input in their development process. Particularly, we observed a low correlation between AQoLS and the social functioning subscore of SF-36 despite a relationship dimension in AQoLS. The difference in instructions, namely "your physical health or emotional problems" in the SF-36 and "your relationship with alcohol" in the AQoLS could explain this discrepancy: some patient could not consider that their relation to alcohol is not part of their physical or mental health, or that the explicit instruction regarding alcohol help patients identifying the impacted domains. As hypothesised, the highest correlation was found between the AQoLS and the mental summary score of the SF-36, which is the score that most often demonstrates

improvement in AUD clinical trials (Luquiens, Reynaud et al. 2012). This is an encouraging argument to support a possible sensitivity to change of the AQoLS in this population.

Even if patients with alcohol use disorders usually consider their condition as more psychological than physical (Daeppen, Krieg et al. 1998), the congruent correlation with several physical sub-scores could be explained by the fact that mental distress can impact physical well-being, for instance in major depressive disorders (Hsu, Sanford et al. 2015). However, no question explored precisely these physical areas.

More surprisingly, general health was inversely correlated to AQoLS. This could be due to a response shift of some severe patients on their general health assessment (Schwartz, Ahmed et al. 2013), which seems not to happen using the AQoLS. Construct validity was explored in a smaller sample (n=60), and even if significance is not the issue of interest in construct validity, results are to be taken with caution due to possible lack of power.

Limitations

Representativeness of the sample is limited due to the refusal to participate of some randomly selected centers. The major limitation of this validation study is that it is cross-sectional, and does not allow testing of the instrument's responsiveness. Therefore, further dynamic validation of the scale is planned. The construct validity of the scale was evaluated in a restricted sample size due to the inclusion in the clinical research form of the other HRQoL scales in a second step, and the comparison of the AQoLS with other related concepts like alcohol-related consequences should be undertaken. The AQoLS was validated using the French version of the scale. A validation of the English version should be performed in the future; however, the simultaneous development of the scale in French and English means that the properties of the two versions are likely to be similar. The AQoLS has also been adapted for use in South Korea, Japan and China (Whalley, Crawford et al. 2014), as well as Germany, and validations of these language versions are planned. Finally, the length of the scale could limit its practicality; moreover, Cronbach's $\alpha > 0.9$, could

translate redundancy in some items. The development of a short version should improve these issues and is planned.

CONCLUSION

The AQoLS is a new instrument to assess HRQOL among patients with AUD from the patients' perspective and presents good psychometric properties. The scale is the only HRQOL instrument specific to patients with AUDs, and was developed based on patients' personal input. This characteristic should allow a more precise and relevant assessment of HRQOL in patients with AUD. The "control" and "self-esteem" dimensions are of particular interest as these concepts are not captured in existing HRQOL instruments used for patients with AUDs. The AQoLS can be used in the context of clinical research. It can provide information about the efficacy of therapeutic interventions regardless of the drinking goal, and demonstrate the interventions' relevance from the patients' perspective. The development of a short version is planned. The AQoLS also could be used in pharmacoeconomic analysis to refine current estimates of the societal burden of AUD. The utility of the AQoLS in routine clinical practice remains to be investigated. Future use of the AQoLS should enable further validation with respect to sensitivity to change.

Table 1: Rotated factorial analysis: factor pattern

Item number – key word	Factor 1: control	Factor 2: self - esteem	Factor 3: relationships	Factor 4: activities	Factor 5: living conditions	Factor 6: negative emotions	Factor 7: sleep
1-everyday activities ^A	0.32		0.51	0.28		0.31	
2- plans ^A	0.28		0.32	0.53			
3- restricted in places ^A	0.31	0.30		0.26			
4- physical activities ^A	0.30			0.64	0.21		
5- jobs around the house ^A	0.27			0.63			
6- ability to work ^A	0.23	0.24	0.31	0.48			
7- cut myself off ^R	0.24	0.46	0.22	0.41			
8- neglected people ^R	0.21	0.26	0.62	0.40			
9- relationships ^R		0.45	0.63		0.30		
10- behaved badly ^R		0.36	0.59				
11- family ^R	0.30	0.30	0.58	0.20		0.24	
12- trust ^R		0.63	0.28		0.21	0.29	
13- sex ^R	0.23	0.40		0.29			
14- friends ^R	0.21	0.65	0.34				
15- household affairs ^{LC}				0.48	0.39		
16- housing situation ^{LC}			0.34		0.50		
17- money spent on alcohol ^{LC}	0.36			0.27	0.61		
18- financial difficulties ^{LC}					0.87		
19- shame ^N	0.22	0.47	0.20			0.42	0.23
20- contempt ^N		0.56	0.25		0.23	0.25	0.26
21- wasting my life ^N	0.40	0.38		0.25		0.36	
22- worried about my health ^N						0.69	
23- worried about my life ^N	0.22	0.23	0.21	0.21		0.71	
24- appetite ^{LAS}	0.30	0.21		0.23	0.26	0.24	0.25
25- appearance ^{LAS}		0.28	0.20	0.33	0.32	0.22	0.23
26- general health ^{LAS}	0.24	0.25	0.26	0.31	0.31	0.28	0.21
27- risky situations ^{LAS}	0.33	0.20	0.50		0.29	0.24	
28- nothing matters ^C	0.74				0.20		
29- alcohol controlled me ^C	0.67		0.22				
30- life around alcohol ^C	0.78			0.22			
31- plan around alcohol ^C	0.76	0.23		0.28	0.20		
32- control of myself ^C	0.62	0.33		0.27		0.20	
33- good night's sleep ^S		0.23				0.21	0.79
34- sleep enough ^S							0.86
Cumulative variance	0.13	0.22	0.31	0.40	0.48	0.54	0.60

Loadings in bold represent the item distribution in the *a posteriori* structure.

Loadings <0.2 are not shown.

Exponent represent a priori structure: ^A: Activities, ^R: Relationships, ^{LC}: Living Conditions, ^N: Negative emotions, ^{LAS}: Looking After Self, ^C: Control, ^S: Sleep.

Table 2 : Construct validity of the AQOLS with SF-36 and EQ-5D (n=60)

	Mean	r
SF-36 ^Δ		
Physical functioning (n=51)	26.51	-0.5
Role functioning/ physical (n=55)	6.11	-0.5
Role functioning/ emotional (n=54)	4.52	-0.5
Energy/fatigue (n=57)	13.74	-0.6
Emotional well-being (n=49)	17.59	-0.4
Social functioning (n=56)	6.02	-0.2
Pain (n=55)	8.77	-0.5
General health (n=53)	14.50	0.3
MCS (n=35)	28.82	-0.7
PCS (n=35)	21.47	-0.1
EQ-5D		
Mobility (n=57)	1.12	0.4
Self-care (n=57)	1.02	0.2
Activity (n=57)	1.31	0.5
Pain (n=58)	1.72	0.2
Anxiety (n=59)	2.05	0.5
Health state visual analogue scale (n=56)	69.23	-0.4

r: spearman correlation coefficient with AQOLS total score

^Δthe lower the SF-36 score the better the quality of life, with the inverse true for the AQOLS

Figures

Figure 1: Flow chart

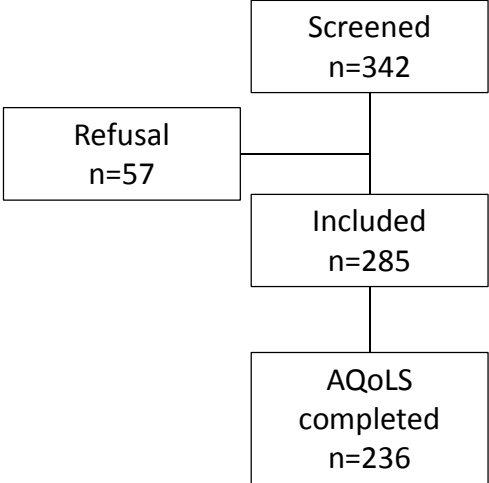


Figure 2: Histogram of AQoLS total score

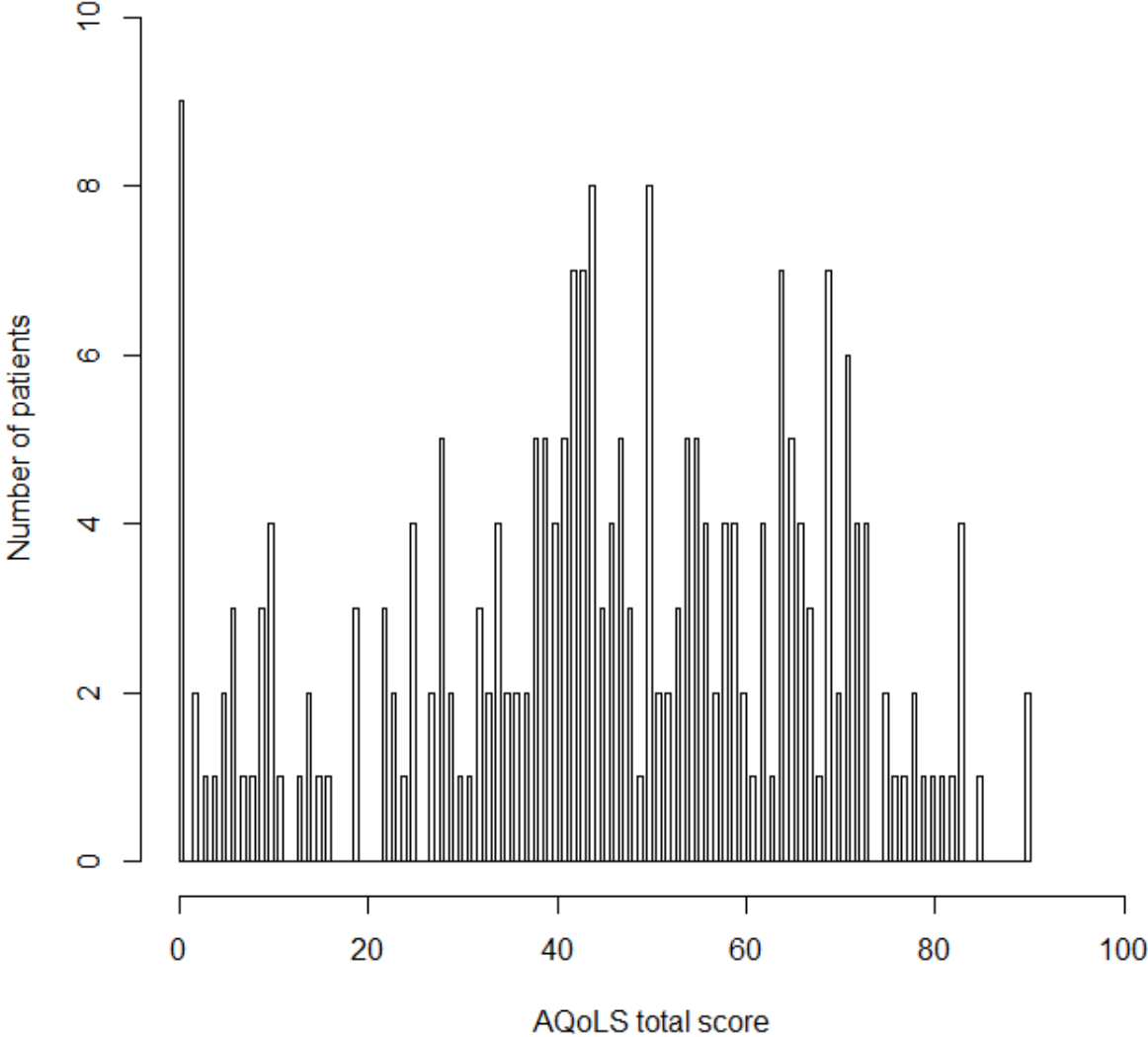
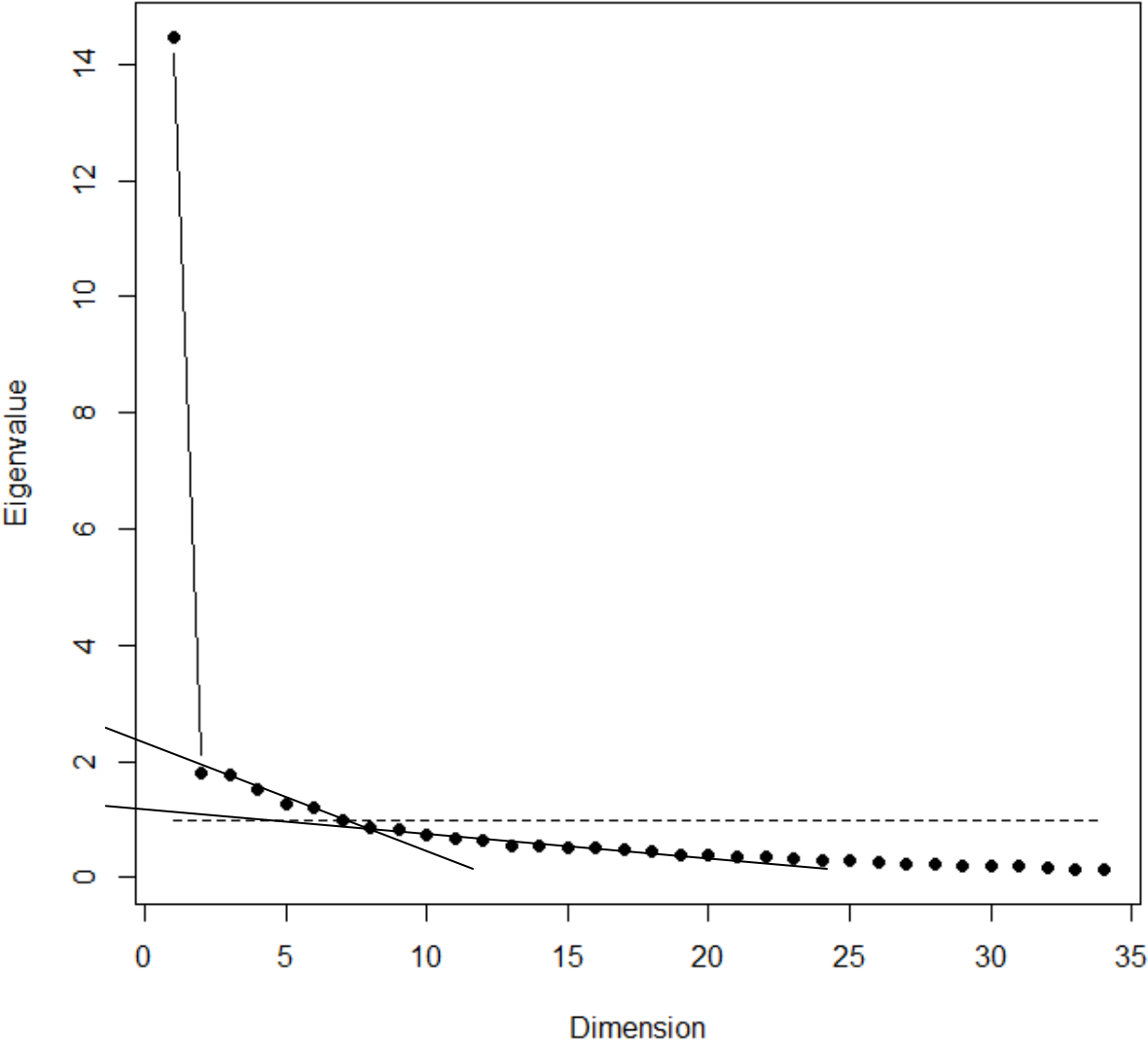


Figure 3 : Scree plot of eigenvalues of AQOLS total score



Acknowledgements

The study was funded by Lundbeck

Compliance with Ethical Standards

- Disclosure of conflicts of interest

HJA has received sponsorship to attend scientific meetings, speaker honoraria, and consultancy fees from Bioprojet, D&A Pharma, Ethypharm, Lundbeck, Merck-Serono, Novartis, and Pfizer.

BF has received sponsorship to attend scientific meetings, speaker honoraria, and consultancy fees from Sanofi, Servier, Pierre-Fabre, MSD, Lilly, Janssen, Otsuka, Lundbeck, Genzyme, Roche, BMS, Novartis, GSK, Pfizer, Celgene, Gilead, Astrazeneka.

PL is an employee of Lundbeck.

AL has received sponsorship to attend scientific meetings from Lundbeck.

JM declares no potential conflict of interest.

FP has received sponsorship to attend scientific meetings, speaker honoraria, and consultancy fees from D&A Pharma, Ethypharm, Lundbeck, Merck-Serono.

JR: reports grants from GWT-TUD and Lundbeck, personal fees and being board member (Nalmefene) for Lundbeck, all outside the submitted work

DW is an employees of RTI Health Solutions.

RTI Health Solutions received funding from Lundbeck to support this study.

- Research involving Human Participants

Prior to initiation of the study, the study protocol was subjected to human ethics and research review by the relevant authorities in each country.

-Informed consent

Each patient signed a consent form to enter the study, after having been given an information notice on the study protocol.

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Adaptations transculturelles: Cultural Adaptation of the Alcohol Quality of Life Scale for Use in Japan, China, and South Korea (Whalley et al, en préparation)

L'article «Whalley, D., S. Crawford, et al. ([DRAFT]). "Cultural Adaptation of the Alcohol Quality of Life Scale for Use in Japan, China, and South Korea."» rédigé pour soumission en anglais est ici synthétisé en français, puis inséré dans sa version complète en anglais.

Si l'échelle AQoLS a d'emblée été développée de manière bilingue français /anglais, une vigilance particulière a été apportée pour éviter tout item spécifique à un pays et à la traductibilité des items, son développement a eu lieu dans un contexte occidental, et il est apparu nécessaire de procéder à une adaptation transculturelle pour son utilisation en Asie. L'article présenté ci-après est donc une adaptation culturelle de l'échelle AQoLS pour le Japon, la Chine et la Corée du Sud.

Méthodes

L'adaptation culturelle de AQoLS a suivi les recommandations pour l'adaptation culturelle de PRO (Wild, Grove et al. 2005). La version anglaise a été utilisée comme version source pour ces trois adaptations. AQoLS a été traduite dans les trois langues par un processus de cinq étapes de traduction -rétrotraduction. Une évaluation par des groupes d'individus représentatifs de la population générale de chacun des trois pays a permis de s'assurer de l'adéquation du contenu et du registre de langage des consignes, items et options de réponse avec chacune des 3 cultures, conduisant à des révisions de la traduction initiale. Puis des entretiens cognitifs de debriefing ont été conduits dans chaque pays auprès de patients avec un trouble d'usage d'alcool actuel ou en rémission, pour s'assurer de la validité de face et de contenu des versions révisées. A chaque étape, une revue était réalisée pour s'assurer de la fidélité de concept avec l'échelle initiale.

Résultats

La traduction a été réalisée sans difficulté, 2 items au Japon, six en Chine et 2 en Corée ont demandé des discussions supplémentaires pour s'assurer du respect de leur signification initiale.

L'évaluation en population générale a été réalisée auprès d'un groupe de cinq en Chine et en Corée et de deux groupes au Japon (cinq et trois patients). Les individus représentatifs de la population générale et sans pathologie majeure ont trouvé la traduction claire et compréhensible et adaptée à leur culture. Onze items ont été révisés dans leur formulation, soit pour ajouter des exemples spécifiques à chaque pays pour aider à expliquer le concept, soit pour adopter une formulation plus fluide. Les deux items ayant posé le plus de difficultés étaient ceux évoquant les tâches ménagères au Japon et les difficultés de logement en Chine. De plus, la consigne a été adaptée en Corée et le mot "alcool" a été remplacé par un mot plus proche désignant une boisson alcoolisée.

Les patients évaluant la version révisée l'ont trouvée claire et proche de leur expérience avec l'alcool. Des modifications ont été apportées à 12 items en tout, concernant là aussi les exemples ou la fluidité de langage, tout en restant fidèle au sens initial. Si les patients japonais étaient tous alcoolodépendants, la moitié des patients chinois et un quart des patients Sud-Coréens souffraient d'un abus d'alcool.

Au total 16 items sur les 34 ont nécessité une modification après l'étape de traduction. Les items les plus problématiques ont été les items 2, 12, 15, et 16 ainsi que les items 3 et 32 en Chine uniquement.

Discussion

L'adaptation transculturelle de AQoLS pour le Chine, le Japon et la Corée du Sud a suivi un processus rigoureux incluant une étape de traduction, d'évaluation en population générale puis par des patients souffrant d'un trouble d'usage d'alcool. L'adaptation simultanée dans

les trois langues a permis de faciliter une harmonisation des trois versions. Une des limites principales est l'absence de patient avec un abus d'alcool inclus pour évaluer la version japonaise. La difficulté à inclure ce type de patient avait déjà été rencontrée lors du développement de l'échelle, qui avait également eu lieu dans un contexte hospitalier pour partie résidentiel. Les trois versions adaptées ont montré une bonne validité de face et de contenu mais il reste à renseigner leurs propriétés psychométriques et à confirmer que la structure validée dans les versions mères est conservée.

Versions japonaise, chinoise et coréenne: voir Annexes 3, 4 et 5

Cultural Adaptation of the Alcohol Quality of Life Scale for Use in Japan, China, and South Korea [DRAFT]

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Declarations of Interest

DW and SRC are employees of RTI Health Solutions. PL is an employee of Lundbeck S.A.S. RTI Health Solutions received funding from Lundbeck S.A.S. for the conduct of this study.

HJA has received sponsorship to attend scientific meetings, speaker honoraria, and consultancy fees from Bioprojet, D&A Pharma, Ethypharm, Lundbeck, Merck-Serono, Novartis, and Pfizer.

ABSTRACT

Purpose

To culturally adapt the Alcohol Quality of Life Scale (AQoLS), a measure of health-related quality of life in alcohol use disorder (AUD), for use in Japan, China, and South Korea.

Methods

The United Kingdom (UK)-English version of the AQoLS was translated into Japanese, Simplified Chinese, and Korean, using forward-back translation. The preliminary translations were assessed by 5 to 8 lay individuals in the three countries, to ensure the cultural appropriateness of language and content. The revised versions underwent cognitive debriefing with 8 to 12 patients with AUD in each country, to ensure the new versions were relevant to the target population.

Results

Preliminary translations were produced with little difficulty. Following the lay assessments, 11 items were modified in one or more of the new versions to improve clarity of the intended concepts and to ensure the translations used natural, everyday expressions. Overall, patients in the cognitive debriefing interviews (Japan: $n = 8$, median age = 56 years, 38% male; China: $n = 10$, median age = 40 years, 80% male; South Korea: $n = 12$, median age = 53 years, 75% male) considered the AQoLS easy to understand and relevant to their experiences with alcohol. Further changes were made to 12 items in one or more versions, to ensure the content was interpreted as intended.

Conclusions

The AQoLS is an appropriate instrument for AUD patients in Japan, China, and South Korea. The new versions were conceptually equivalent to the source UK-English version and had good face and content validity.

INTRODUCTION

Alcohol use disorder (AUD) is defined as a problematic pattern of alcohol use leading to clinically significant impairment or distress occurring within a 12-month period. AUD is characterised by a cluster of behavioural and physical symptoms that can include withdrawal, tolerance, and craving [1]. Although alcohol abuse and dependence were previously considered as two distinct disorders, the latest edition of the *Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)* (DSM-5) defines a single diagnosis of AUD, with mild, moderate, and severe disorder subclassifications [2]. The diagnostic criteria for AUD in DSM-5 represent an amalgamation of the previous criteria for alcohol abuse and dependence defined by the *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)* (DSM-IV), with the addition of craving symptoms [2].

It is estimated that 3.6% of the world's population has a current AUD [3, 4]. Worldwide, alcohol is the third leading cause of disability and is associated with considerable morbidity and mortality [5]. In East Asian countries, alcohol has been an important part of religious and cultural rituals for centuries, and alcohol continues to be an integral part of everyday social interactions, such as social celebrations and business negotiations [6, 7]. In countries such as Japan, China, and South Korea, the increase in alcohol consumption and the diversification of the traditional alcohol-consuming population to include non-drinkers (e.g., women, young people, and the elderly) has resulted in the increased prevalence of AUD, with associated implications for health and social well-being [7, 8].

In their 2014 global report on alcohol and health, the World Health Organization presented 12-month prevalence estimates for AUD (which included alcohol dependence and harmful use of alcohol): 11.1% for the United Kingdom (UK), 7.5% for Europe, and 7.4% for the United States [5]. Equivalent estimates for East Asia were 2.8% in Japan, 4.9% in China (4.9%), and 6.2% in South Korea, although studies have further highlighted considerable

within-country regional variations, particularly across different provinces in China [8, 9, 10, 11].

The rising levels of alcohol consumption and increased AUD prevalence rates in Japan, China, and South Korea are a major public health concern and have considerable socio-economic implications [8, 12, 13]. Only an estimated 5% of patients with AUD in Japan receive some form of medical care, either psychosocial therapy or pharmacological treatment [14]. While pharmacological treatment in Japan is limited, it is expected to become more accessible; there is considerable interest in medications that reduce alcohol consumption [14]. The percentage of patients receiving treatment for AUD has been reported as being similarly relatively low in China and South Korea [11, 12].

Regardless of the disparate societal norms concerning the consumption of alcohol, the breach or abuse of culture-specific boundaries involving the use of alcohol has considerable social ramifications, including the potential for the breakdown of family relationships, reduced work productivity, and social marginalisation [5, 15]. Excessive alcohol consumption also is strongly related to a wide range of mental health problems, including depression and anxiety [15]. Furthermore, AUD (either alcohol abuse or dependence) has been shown to be associated with poorer health-related quality of life (HRQOL) compared with a normal population [16]. The impact of AUD on the individual goes beyond the immediate symptoms and the quantity of alcohol consumed, which are assessments commonly used as primary endpoints in clinical trials [17].

In alcohol research, HRQOL is considered to be an important outcome to evaluate treatment success, as it can provide a more holistic assessment of the impact of AUD beyond that which is measured by clinical factors alone [18]. The Alcohol Quality of Life Scale (AQoLS) is a new, patient-reported outcome (PRO) measure for use in AUD, developed to address the paucity of instruments specifically designed to assess HRQOL in this patient group [19]. The AQoLS was developed in parallel in the UK and France, using a comprehensive

development methodology. A previous systematic review of HRQOL instruments used in alcohol-dependence clinical trials [20] was used to inform the initial conceptual framework for the instrument. The items were generated from concept elicitation focus groups with patients with AUD and underwent expert review by clinicians in the UK and France to ensure their clinical relevance. The draft questionnaire was subsequently refined and evaluated for face and content validity through two rounds of cognitive debriefing interviews with patients with AUD. The development process also included a translatability assessment to ensure that the items of the AQoLS were potentially amenable to future cultural adaptation.

The aim of the current study was to produce three new language versions of the AQoLS for use in Japan, China, and South Korea.

METHODS

The cultural adaptation (including translation and linguistic validation) of the AQoLS for Japan, China, and South Korea followed recommended industry standards [21], with additional elements to ensure that the target concepts were adequately expressed in all language versions while maintaining conceptual equivalence with the source version. The AQoLS was developed simultaneously in the UK and France; the UK-English version was used as the source version for all new language adaptations, to ensure consistency.

The AQoLS

The AQoLS is composed of 34 items across seven domains: Relationships, Activities, Looking After Self, Emotional Impact, Control, Living Conditions, and Sleep. Each item has four response categories (“not at all”, “a little”, “quite a lot”, and “very much”), with a 4-week recall period.

An Instrument Codebook was developed as a reference document to facilitate the production of the new language versions of the AQoLS. The document described the conceptual

meaning of each item and instruction, together with specific guidance for translating elements of the measure.

Stages in the Cultural Adaptation of the AQoLS

The cultural adaptation process involved three key stages in each of the target countries: translation, lay assessment, and patient review. These stages are described in the following subsections.

Stage 1: Translation

The initial translation of the UK-English version of the AQoLS into the three languages (Japanese, Simplified Chinese, and Korean) was conducted using a five-stage, forward-back translation methodology: forward translation, reconciliation, backward translation, backward translation review, and conceptual equivalence review.

Stage 2: Lay Panel Assessment

Lay panel assessments were held with groups of individuals drawn from the general population in each of the three countries. The purpose of these assessments was to ensure the cultural appropriateness of the instrument (including the instructions, items, and response options) in terms of the language register and content. Each panel was led by an experienced in-country facilitator and took the form of a group discussion. Participants were asked to comment on the following: whether the wording was clear and used natural, everyday language; whether anything in questionnaire was confusing, inappropriate or difficult to understand; whether the content of the items was suitable; and whether any changes would improve the wording. Revisions were made to the initial translations based on feedback from the lay assessment group in each country.

Stage 3: Patient Review

Individual cognitive debriefing interviews were conducted with AUD patients in each country to assess the face and content validity of the revised translated versions of the AQoLS.

Interviews were conducted face to face and led by an experienced interviewer in each country. After each stage, a detailed conceptual review of the back translations and source materials was undertaken to ensure that the target concepts from the original measure were maintained.

Patients and Setting

Lay Assessment General Population Samples

Participants in the lay panel assessments were recruited to be representative of the general lay population in each of the three cultures in terms of age, sex, and socio-economic status. Each panel was conducted as a face-to-face group meeting in each of the three countries.

Cognitive Debriefing Interview Patient Samples

Three clinical sites, one in each country, were used to recruit patients for the cognitive debriefing interviews: National Hospital Organization Kurihama Medical and Addiction Center in Japan, Changsha Xiang Ya No. 2 Hospital in China, and Yangsan Hospital in South Korea.

The inclusion and exclusion criteria for patient recruitment mirrored that used in the original development of the AQoLS (see Box 1). The primary diagnostic criteria was alcohol abuse or dependence (either current or remitted) as defined by criteria from DSM-IV and assessed by the Mini-International Neuropsychiatric Interview version 6.0 [22]. Two supplemental questions were added to further categorise patients' AUD as current (i.e., the presence of diagnostic symptoms in the last month) or in remission and to assess the presence of cravings for alcohol within the previous 12 months. The addition of the question on craving was in line with the updated DSM-5 diagnostic criteria for AUD.

Patients were recruited to represent a range of sociodemographic and AUD characteristics. Interviews were conducted at the respective clinical site in each country.

Ethics and Research Approvals

Prior to initiation of the study, ethical approval was obtained from the relevant authorities in Japan, China, and South Korea. The study also was reviewed and granted approval by one of RTI International's institutional review boards.

RESULTS

Translation (Stage 1)

The preliminary translations of the AQoLS into Japanese, Simplified Chinese, and Korean were produced with little difficulty. Individual items (two items in Japan, six items in China, and two items in South Korea) required additional review and discussion, either during initial translation and reconciliation or in the subsequent back-translation review. The key discussions around the preliminary translations in each of the countries focused on the selection of culturally appropriate words and phrases that would clearly express the original meaning of the source items and ensure they would be interpreted as intended in each country. Where a consensus item translation could not be agreed upon, alternative formulations were taken forward for evaluation in the lay assessment (two items each in China and South Korea).

Lay Panel Assessment (Stage 2)

Panel Samples

One lay panel was conducted for China and South Korea, and each was composed of five individuals. Two lay panels were held in Japan; the first included five individuals, and the second consisted of three individuals, to ensure adequate representation of the lay population in terms of occupational and educational background. All lay panel participants were native speakers of the respective language, and none reported a major morbidity. The demographic characteristics of the participants are shown in Table 1.

[TABLE 1 HERE]

Key Findings From the Lay Panel Assessments

Participants in the lay panels in each of the three countries generally found the respective preliminary translations of the AQoLS to be clear, easy to understand, and appropriate to their culture. Modifications were made to 11 items in one or more country: 3 items in Japan, 8 items in China, and 3 items in South Korea (Table 2). Reasons for the changes made to items included the following:

The addition of country-specific examples to help explain a target concept, or the change of existing examples to be more culturally appropriate

The addition or modification of individual words or phrases to use a more natural expression or to ensure that the intended meaning was more accurately or clearly conveyed

The production of an alternative version of the item for further testing or the selection between previously derived alternative formulations. The phrases that presented most difficulty in the lay panels were 'household affairs' in Japan and 'housing situation' in China. Modifications and alternative translations were suggested in order to find more natural expressions of these items without distorting the original concept of the source items. In addition, a key modification made to the Korean version was the replacement of the preliminary translation for 'alcohol' with the Korean word for 'liquor'; the former was considered by the lay panel as relating more to industrial rather than consumable alcohol and thus unsuitable.

[TABLE 2 HERE.]

Patient Review (Stage 3)

Between 8 and 12 patients with AUD were recruited to participate in the cognitive briefing interviews in each country. Table 3 presents the demographic and AUD characteristics of the patient samples in Japan, China, and South Korea. Patients represented a range in terms of demographic and AUD status. For comparison, the table also presents the patient characteristics of the concept elicitation focus groups and cognitive debriefing interviews

from the original development of the AQoLS in the UK and France [19]. As in the original development, the majority of patients in Japan, China, and South Korea met the criteria for alcohol dependence, with few patients meeting the diagnosis of alcohol abuse only.

[TABLE 3 HERE.]

Key Findings From the Cognitive Debriefing Interviews

Overall, patients in each of the three countries found the AQoLS easy to understand and considered the content relevant to their experiences with alcohol. Changes made as a result of the lay assessment panels were generally well accepted. Further changes were made to a total of 12 items across the three versions: 5 items in Japan, 6 items in China, and 5 items in South Korea. As with the lay assessment, changes made related to modifications or additions to item examples, modifications to individual words or phrases to clarify meaning or improve immediacy of the language, and the selection between alternative translations of individual items. For example, substantial revisions were required for item 3 in the Chinese version (“I have been restricted in the places I can go because of alcohol”), which continued to be misinterpreted by patients. In South Korea, the translation of ‘housing situation’ was not interpreted as intended by patients, and further changes were made to this wording. These changes were tested with small convenience samples of lay individuals in the respective countries, and the items were interpreted as intended.

Overview of Changes Made to the AQoLS Items During Cultural Adaptation

After the initial translation stage and following the results of the lay panel assessment and the cognitive debriefing interviews, a total of 16 of the 34 items in the AQoLS required modification in one or more of the three countries (Table 2). The most changes needed were to the Simplified Chinese version: 10 items required modification, compared with 7 items each to the Japanese and Korean versions. The most problematic items in the three versions, i.e., those generating the greatest discussion to produce the most appropriate

translation, were items 2, 12, 15, and 16, as well as items 3 and 32 in China alone. Changes were made to these items following both lay assessment and patient review.

The case example of item 2 (“It has been difficult for me to follow through on plans”) from the Chinese cultural adaptation is presented to illustrate the roles of the lay panel assessment and the patient review in the cultural adaptation process. The overall meaning of this item was specified in the Instrument Codebook as, “The respondent has found it hard to take plans through to completion.” Additional explanations were given for the phrases ‘to follow through’ (“to act and complete on something”) and ‘plans’ (“activities, events or commitments that are pre-arranged”). Figure 1 illustrates the changes that were made to this item at each adaptation stage. The translators were unable to agree on a consensus translation and thus produced two alternative translations for further consideration. The lay assessment panel gave their opinion on the most appropriate version from a language and cultural perspective, and a single translation was selected. The patient review subsequently resulted in further changes to the item, to account for the patient perspective on the underlying concept. Specifically, the wording was changed to ensure that the notion of pre-arranged plans, as specified in the Instrument Codebook, was conveyed rather than the aim of stopping drinking.

[FIGURE 1 HERE.]

DISCUSSION

The impact of AUD and its treatment on an individual’s quality of life is an important outcome in alcohol research [18]. Clinical assessments of alcohol consumption used in clinical trials do not capture the humanistic burden of AUD from the patient perspective; moreover, such assessments are considered to be poor predictors of treatment efficacy [18]. The AQoLS is the first measure specifically developed to assess the HRQOL impact of AUD [19]. The instrument was intended for use in international studies and thus was developed simultaneously in the UK and France to avoid the inclusion of concepts that were

idiosyncratic to a single culture. Furthermore, a formal translatability assessment was included in the item selection process to maximise the potential cross-cultural applicability of the instrument's content, thus facilitating future cultural adaptations.

This study reports on the production of the first new language versions of the AQoLS following its initial development. Preliminary translations of the UK-English AQoLS into Japanese, Simplified Chinese, and Korean were produced with little difficulty. Further refinements were made following the lay panel assessments and the patient cognitive debriefing interviews to ensure that conceptual equivalence with the source version was maintained and that participants interpreted the target concepts as intended. These assessments further demonstrated that the new language versions were culturally appropriate and that the AQoLS has face and content validity for patients with AUD in each of the three countries.

Cultural Adaptation of PRO Instruments

The cultural adaptation of PRO instruments necessitates the application of rigorous methods to achieve conceptual equivalence with the original source instrument and to express the content in everyday language appropriate to the target culture [23]. Concepts such as symptoms and some aspects of functional status are relatively straightforward to translate because they are less likely to be bound by societal and cultural norms. In contrast, HRQOL measures can contain complex and more abstract concepts that are potentially more difficult to translate directly into different cultures and languages. A literal translation of the source text for instruments is less likely to either express the conceptual meaning of the source text accurately or take into account the linguistic and cultural nuances of the target country [24]. In recognition of this, the focus of cross-cultural adaptation of PRO instruments is on attaining semantic and/or conceptual comparability, as well as ensuring cultural relevance, rather than maintaining linguistic equivalence [25].

The cultural adaptation of PRO instruments generally follows standard translation guidelines that involve forward-back translation, followed by the testing of the new language version with patients from the target culture [21]. Such methods are likely to be adequate for simple PRO concepts or in instances where the target language and culture are similar to those of the source instrument version, for example, across different European languages. However, many different recommended processes for cross-cultural adaptation exist [25] and there have been examples where standard methods have been lacking. For example, the cultural adaptation of the SF-36 Health Survey (SF-36) from American English to Japanese [26] followed the guidelines set by the International Quality of Life Assessment (IQOLA) network [27]. A preliminary Japanese version was produced following forward-back translation and then psychometrically evaluated. The results of the preliminary psychometric evaluation yielded inconsistent results, leading the authors to suggest that there were problems with the preliminary translation in relation to the meaning and level of severity conveyed by the translated items and/or response options. These issues were subsequently explored through focus groups, resulting in a revised translation that was shown to have acceptable psychometric properties. Thus, although the first Japanese translation of the SF-36 was fully compliant with the IQOLA guidance, it did not produce a culturally appropriate translation that maintained the intended meaning of the source instrument. The authors attributed this to the magnitude of linguistic and cultural differences between Japan and the United States [26]. The AQoLS cultural adaptations in Asia have been methodologically designed and processed to palliate this issue.

Cultural Adaptation of the AQoLS

The methodology employed to adapt the AQoLS for use in Japan, China, and South Korea was designed to build on generally accepted standards for the translation and linguistic validation of PRO instruments [21] by incorporating a lay assessment as an additional stage. This supplementary step involved the review of the preliminary translated measure by healthy individuals who were representative of the lay populations of the three countries.

Such a review facilitated the early identification of any issues specifically related to cultural norms or the level of language used. The addition of such a lay assessment to the standard language adaptation approach is vital for instruments that include multiple domains assessing complex concepts, as is the case in many HRQOL measures, or for where adaptation is across disparate languages and cultures.

Given the complexity of AUD and thus the complexity required of an instrument to measure its impact, it was vital that care was taken during the development of the AQoLS to ensure cross-cultural applicability. The simultaneous development of the measure in the UK and France, together with the formal translatability assessment undertaken during the item selection process, was designed to minimize ethnocentricity and facilitate the production of subsequent language versions.

The additional component of the lay assessment in the cultural adaptation process allowed attention in the cognitive debriefing interviews to concentrate on experiential issues relating to the relevance and appropriateness of the items to patients' experiences of AUD, rather than on linguistic or cultural issues associated with wording. In this way, the content of the cognitive debriefing interviews in Japan, China, and South Korea were more in line with that of the interviews conducted during the original instrument development and facilitated a more focused assessment of content validity.

Strengths and Limitations of the Study

The study used rigorous methodology in accordance with recommended industry standards [21] and contained an additional element (the lay assessment) designed to facilitate the appropriate adaptation of more complex concepts, which are often reflected in HRQOL measures, across disparate languages and cultures. Furthermore, an in-depth conceptual review of the back translation and source materials was conducted by the authors involved in the original instrument development after each stage in the adaptation process, to ensure that the intended meaning of the original concepts was maintained. The simultaneous

production of the three language adaptations also facilitated harmonization across the three versions.

A key limitation of the study was that the clinical site in Japan was unable to recruit patients who met the criteria for alcohol abuse. This paralleled the difficulties encountered during the original development of the AQoLS in the UK and in France, and is considered characteristic of patients presenting for treatment in clinical practice in the countries concerned. Nonetheless, patients who met the criteria for alcohol abuse were recruited for the cognitive debriefing interviews in China and South Korea, and the measure was found to be relevant and acceptable to those patients. This suggests that the AQoLS is acceptable for patients with milder classifications of AUD.

Further Validation of the AQoLS

This study has shown that the new Japanese, Simplified Chinese, and Korean language versions of the AQoLS to be appropriate and to have good face and content validity with AUD patients in the three countries. It still remains necessary to establish the psychometric properties in terms of test-retest and internal consistency reliability, construct validity, and responsiveness of these new language versions. In addition, psychometric techniques, such as item-response theory, could be applied to explore the measurement equivalence of these new language versions, as well as the original UK-English and French versions.

Conclusion

The AQoLS is a new instrument designed specifically to assess HRQOL in AUD. The new language versions for Japan, China, and South Korea have proven to be conceptually equivalent to the original UK-English version and to have good face and content validity in their respective countries. This study has shown that the AQoLS is an appropriate instrument with which to assess HRQOL in AUD patients in Japan, China, and South Korea.

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Tables and Figures

Box 1 Inclusion and Exclusion Criteria for Patient Samples

Inclusion criteria:

- (1) Patient meets the clinical diagnostic criteria of current or remitted alcohol abuse or dependence, as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, and assessed with the Mini-International Neuropsychiatric Interview (version 6.0)^a
- (2) Patient is aged 18 years or older (China and South Korea) or 20 years or older (Japan)^b
- (3) Patient has the cognitive ability to participate in a cognitive debriefing interview (as judged by the clinical team)
- (4) Patient is able to provide written informed consent

Exclusion criteria:

- (1) Patient has learning difficulties that prevent him or her reading and responding to questionnaires
- (2) Patient has a major physical comorbidity judged by the clinical team to be a significant influence on the patient's day-to-day life (e.g., liver failure)
- (3) Patient has another axis 1 diagnosis (with the exception of nicotine dependence), as judged by the clinical team
- (4) Patient is judged by the clinical team to be incapable of participating in the study (e.g., if the patient is unable to give fully informed consent)
- (5) Patient is currently taking a drug used off-label for the treatment of alcohol abuse or dependence
- (6) Patient is currently undergoing acute withdrawal treatment or is experiencing acute withdrawal symptoms judged by the clinical team to be a significant influence on the

patient's day-to-day life, and that is likely to continue to the time of study participation

(7) Patient has significant cognitive impairment, as judged by the clinical team and, for participants in the cognitive debriefing interviews, evaluated with the Mini-Mental State Examination

AUD = alcohol use disorder.

^a Two supplemental questions were added to categorise patients' AUD as current (i.e., the presence of diagnostic symptoms in the last month) or in remission and to assess the presence of cravings for alcohol within the previous 12 months.

^b The criterion of 20 years of age was considered more appropriate in Japan to reflect the legal drinking age.

Table 1 Sample Characteristics of the Lay Panel Participants

Sample Characteristic	Japan (n = 8)	China (n = 5)	South Korea (n = 5)
Age, years			
Median	34.0	42.0	45.0
Range	20-59	27-50	39-65
Sex, n			
Male	4	3	3
Female	4	2	2

Table 2 Items of the AQoLS Modified During the Lay Assessment and the Patient Review

AQoLS Item Number and Text	Countries in Which Modifications Were Made	
	Lay Assessment	Patient Review
1. I have felt I miss out on everyday activities with family and friends		
2. It has been difficult for me to follow through on plans	China	Japan, China
3. I have been restricted in the places I can go because of alcohol	China	China
4. I have struggled doing physical activities due to alcohol (e.g., DIY, walking, cycling)	China	South Korea
5. It has been too much effort to do jobs around the house due to alcohol (e.g., cleaning, gardening, maintaining the house)	China	
6. Alcohol has interfered with my ability to work		
7. I have cut myself off from other people	South Korea	
8. I have neglected the people close to me	China, South Korea	
9. Alcohol has damaged my close relationships		Japan, South Korea
10. I have behaved badly towards other people		
11. I have felt I miss out on family life because of alcohol		

AQoLS Item Number and Text	Countries in Which Modifications Were Made	
	Lay Assessment	Patient Review
12. I have felt that people have no trust in me	China, South Korea	China, South Korea
13. Alcohol has interfered with my sex life		
14. Alcohol has interfered with my relationships with friends		
15. I have struggled to keep on top of my everyday household affairs (e.g., dealing with mail, organising appointments)	Japan	Japan, China
16. Alcohol has had a negative effect on my housing situation	Japan, China	South Korea
17. All my money has gone on alcohol		Japan
18. Alcohol has caused me financial difficulties		South Korea
19. I have felt ashamed of myself		
20. I have felt that people look down on me		
21. I have felt that I am wasting my life		
22. I have worried about the effect alcohol has been having on my health		
23. I have worried about alcohol causing problems in my life		
24. I have had no appetite		

AQoLS Item Number and Text	Countries in Which Modifications Were Made	
	Lay Assessment	Patient Review
25. I have neglected my appearance		
26. I have neglected my general health		
27. I have put myself in risky situations		Japan
28. I have felt that nothing matters more than alcohol		
29. Alcohol has controlled me		China
30. My life has revolved around alcohol		
31. I have planned my days around alcohol		
32. I have felt as though I have not been in control of myself	China	China
33. I have not had a good night's sleep		
34. I have not been getting enough sleep	Japan	

AQoLS = Alcohol Quality of Life Scale; DIY = do it yourself.

Table 3 Sample Characteristics of Patients Participating in the Cognitive Debriefing Interviews

Characteristic	AQoLS Cultural Adaptation Samples			AQoLS Instrument Development Samples ^a			
	Japan (n = 8)	China (n = 10)	South Korea (n = 12)	UK Concept Elicitation (n = 17)	UK Cognitive Debriefing (n = 17)	France Concept Elicitation (n = 21)	UK Cognitive Debriefing (n = 14)
Age, years							
Median	56.0	40.0	53.0	42.0	46.0	48.0	47.5
Range	34-71	25-45	44-65	23-65	29-72	31-69	32-57
Sex, n							
Male	3	8	9	12	12	14	10
Female	5	2	3	5	5	7	4
DSM-IV diagnosis,^b n							
Dependence	8	5	9	17	17	21	13
Abuse							
Abuse	0	5	3	0	0	0	1
MINI dependence score^c							
Median	5.5	5.0	6.0	6	6	5	6
Range	3-7	4-7	4-7	4/7-7/7	3/7-7/7	3/7-7/7	3/7-7/7
MINI abuse score^d							
Median	N/A	2.0	2.0	N/A	N/A	N/A	3
Range	N/A	1-2	1-4	N/A	N/A	N/A	3/4
Current AUD status, n							
Current	3	6	4	8	12	12	8

	AQoLS Cultural Adaptation Samples			AQoLS Instrument Development Samples ^a			
	Japan (n = 8)	China (n = 10)	South Korea (n = 12)	UK Concept Elicitation (n = 17)	UK Cognitive Debriefing (n = 17)	France Concept Elicitation (n = 21)	UK Cognitive Debriefing (n = 14)
Character- istic Remitted	5	4	8	9	5	9	6

AQoLS = Alcohol Quality of Life Scale; AUD = alcohol use disorder; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)*; MINI = Mini-International Neuropsychiatric Interview; N/A = not applicable, UK = United Kingdom.

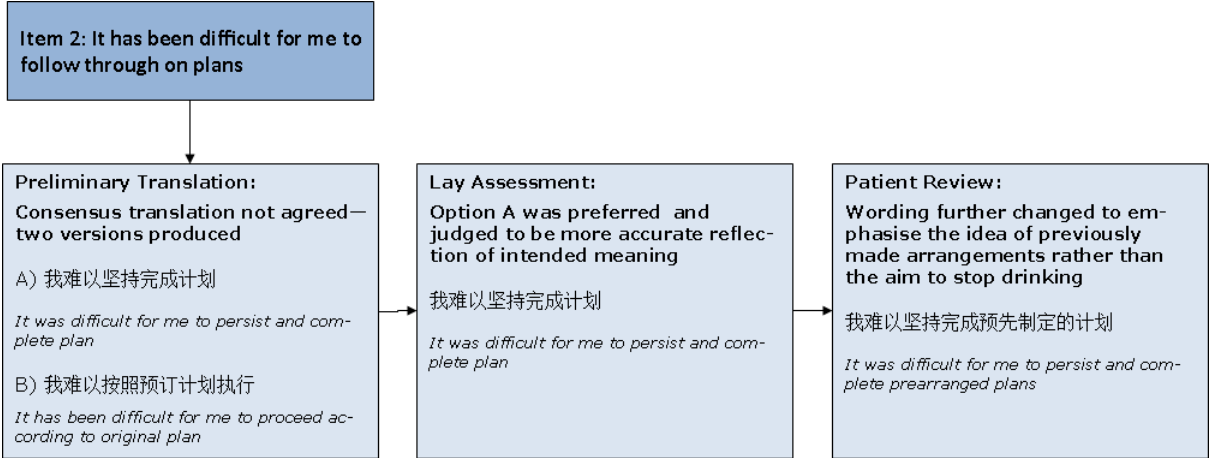
^a Source: [19].

^b Assessed by the MINI 6.0 [22].

^c MINI dependence score is the number of dependence criteria met; scores can range from 0 to 7, with a minimum of 3 representing a diagnosis of alcohol dependence.

^d MINI abuse score is the number of abuse criteria met; scores can range from 0 to 4, with a minimum of 1 representing a diagnosis of alcohol abuse in the local countries.

Fig. 1 Translation and Adaptation of Item 2 of the AQoLS in Simplified Chinese



AQoLS = Alcohol Quality of Life Scale.

Perspectives :

- Validation en population étudiante de l'échelle AQoLS et étude de l'impact du binge drinking sur la qualité de vie

Le travail de validation présenté dans cette thèse a été réalisé en population clinique adulte. Il est important de connaître le comportement et les caractéristiques de l'échelle dans d'autres populations d'intérêt, notamment la population estudiantine, particulièrement exposée aux consommations d'alcool, notamment en mode binge-drinking. Nous avons donc réalisé une enquête transversale non interventionnelle, en ligne, auprès de 17439 étudiants français en études supérieures, inscrits en université ou en grande école. Cette enquête avait trois objectifs : (1) étudier le comportement de binge drinking et son impact sur la qualité de vie, (2) valider et adapter à la population générale estudiantine et aux jeunes binge drinkers l'échelle AQoLS, (3) étudier la relation entre l'identité de « buveur », le binge drinking et l'impact sur la qualité de vie. Ces données sont en cours d'analyse. L'annexe 6 présente la liste des établissements ayant participé à l'enquête et les taux de participation.

[Annexe 6: Enquête BDmiE (Binge Drinking en milieu Etudiant) Comment va ma vie...avec l'alcool ? : établissements participants et taux de réponse]

- Validation de la version allemande d'AQoLS

Afin d'étendre l'utilisation de l'échelle, une traduction-rétrotraduction l'échelle AQoLS a été réalisée par Jürgen Rehm et Jakob Manthey. La version allemande d'AQoLS, en annexe 7, a été proposée à 803 patients allemands en soins primaires ou spécialisés, suivis depuis un an, en rémission ou non (Etude européenne APC). Ces données sont en cours d'analyse et permettront de confirmer la structure d'AQoLS dans sa version allemande et connaître les propriétés psychométriques et la validité de construit de cette version.

[Version allemande: annexe 7]

- Transformation en score d'utilité

Dans le cadre de l'étude citée ci-dessus, nous disposons également d'une mesure directe de l'utilité par la méthode du pari standard, consistant à demander quel est le « sacrifice » que des personnes seraient prêtes à accepter pour recouvrer une parfaite santé. Nous pourrions ainsi estimer des scores d'utilité indiquant l'intensité des préférences des personnes pour les états de santé correspondant aux différents niveaux de qualité de vie mesurés par AQoLS. (Etude européenne APC, n=803).

- Documentation de la sensibilité au changement de AQoLS

Le travail de validation présenté dans cette thèse a été réalisé de façon transversale, et nous ne disposons pas jusqu'à présent de données sur la sensibilité au changement de l'échelle. L'Etude PACT, planifiée par les laboratoires Lundbeck pour un recrutement en janvier 2016 en milieu de soins primaires, proposera une complétion de AQoLS à 6000 sujets présentant un trouble d'usage d'alcool à l'inclusion, un mois, deux mois, trois mois et six mois. Cette étude permettra de renseigner sur la sensibilité au changement de AQoLS. ,

- Validation de la version courte d'AQoLS, à 7 items (étude APC + étude PACT)

Cette même étude permettra de disposer d'un nouvel échantillon pour réduire l'échelle et valider une version courte à 7 items, un item par dimension, afin de rendre son utilisation plus aisée.

- Etude des liens avec le craving (étude SELECT)

L'étude SELECT planifiée par les laboratoires Lundbeck en 2016, permettra d'explorer les liens entre AQoLS (dans une version courte) et le craving.

- **Validation en population âgée**

Comme précisé précédemment, il est important de connaître les caractéristiques psychométriques de AQoLS dans des populations spécifiques, comme la population âgée. Nous proposerons un projet pour la campagne de PHRC-N en 2016 en ce sens.

- **Validation des versions asiatiques**

Les validations des versions chinoises, japonaises et coréennes de AQoLS sont programmées au sein d'études observationnelles planifiées par Lundbeck.

- **Développement d'un instrument de mesure de la qualité de vie spécifique à l'addiction aux jeux de hasard et d'argent suivant la même méthodologie**

Une revue de la littérature (non publiée, N Bonfils), a permis de constater qu'il n'existait pas d'échelle de qualité de vie liée à la santé spécifique aux joueurs problématiques et pathologiques. Nous prévoyons dans le cadre du Master 2 pour l'année 2015-2016 de M. Nicolas Bonfils, encadré par A Luquiens et HJ Aubin, d'appliquer la méthodologie centrée sur le patient qui a permis de construire l'échelle AQoLS pour développer un instrument de mesure de la qualité de vie spécifique à l'addiction aux jeux de hasard et d'argent. Ce projet a obtenu un financement par la fondation des gueules cassées.

Conclusion

Le travail présenté ici est fondé sur un triple constat clinique: le faible recours au soin, la difficulté d'alliance thérapeutique, un certain manque de concordance entre les objectifs du thérapeute et du patient, et d'un contexte particulier de changement de paradigme dans l'appréhension des objectifs thérapeutiques. Celle-ci a d'abord amené à intégrer différents objectifs de consommations comme possibilités de cible thérapeutique (abstinence versus réduction de consommation), puis à une prise de distance vis-à-vis de cette notion pour envisager les modifications de consommations d'alcool comme les moyens d'améliorer le vécu du patient, et donc sa qualité de vie. Mais il s'agit surtout d'une initiative faisant partie de l'intégration de la démarche des soins centrés sur le patient à l'alcoologie. Nous avons pu mettre en évidence le caractère imparfait des instruments utilisés jusqu'à présent pour mesurer la qualité de vie liée à la santé des patients souffrant d'un trouble d'usage d'alcool, et établir la nécessité de développer un instrument rapporté par le patient, spécifique au trouble d'usage d'alcool, mesurant l'impact de l'alcool sur la qualité de vie. Nous avons développé l'échelle AQoLS répondant à ces caractéristiques, selon les recommandations actuelles pour le développement des PRO, avec une contribution extensive des patients. L'échelle AQoLS est donc issue directement du point de vue des patients, qui a été détaillé dans un article complémentaire (Luquiens, Owens et al. [DRAFT]), explorant le concept de qualité de vie dans le trouble d'usage d'alcool en présence de différences socio-culturelles. Nous avons identifié un contenu non spécifique à un pays et facilement traductible, et ainsi déjà permis sa traduction en allemand et son adaptation dans trois pays asiatiques, la Chine, le Japon et la Corée du Sud. Nous disposons d'une validation transversale de l'échelle AQoLS, montrant une structure à sept dimensions: activités, relations interpersonnelles, émotions négatives, estime de soi, contrôle, sommeil, conditions de vie. Les 34 items ont été conservés, et la possibilité de sommer les items pour obtenir un score total confirmée. L'échelle AQoLS s'est montrée corrélée modérément et congruement aux deux échelles génériques de QVLS les plus utilisées. Les prochaines étapes principales sont la

documentation de la sensibilité au changement de l'échelle, et la validation d'une version courte à 7 items, prévues toutes les deux en 2016. La validation de l'échelle dans des populations plus spécifiques (jeunes et âgées) est en cours d'analyse pour la première et prévue pour la seconde.

L'échelle AQoLS donne la perspective, au sein d'études interventionnelles ou observationnelles à venir, d'une documentation plus pertinente du point de vue des patients de l'efficacité des interventions en alcoologie.

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ANNEXES

Annexe 1: AQoLS version française

Échelle de Qualité de Vie (AQoLS)

Merci de bien vouloir lire les instructions attentivement

Le but de ce questionnaire est d'évaluer l'impact qu'a eu l'alcool sur votre vie **au cours des 4 dernières semaines**. Merci de vous rappeler de ne pas répondre pour une période qui dépasse **les 4 semaines**.

Dans ce questionnaire le mot 'alcool' sera utilisé pour décrire votre relation avec l'alcool dans son ensemble, indépendamment du fait qu'actuellement vous buvez ou non.

Veillez choisir pour **chaque** affirmation la réponse qui correspond le mieux à votre situation.

S'est appliqué à moi au cours des 4 dernières semaines ...

	Pas du tout	Un peu	Beaucoup	Énormément
1. J'ai eu l'impression de passer à côté d'activités de tous les jours avec ma famille et mes amis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Il m'a été difficile d'aller au bout des mes projets	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. J'ai été limité(e) dans les endroits où je pouvais aller à cause de l'alcool	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. J'ai eu du mal à effectuer des activités physiques à cause de l'alcool (ex : bricolage, marche, vélo)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. A cause de l'alcool, l'entretien de ma maison m'a demandé trop d'effort (ex : faire la vaisselle, la lessive, faire le ménage, changer une ampoule, le jardinage).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. L'alcool a nui à ma capacité de travail	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Merci de tourner la page

Veillez vous rappeler de répondre **seulement sur les 4 dernières semaines.**

S'est appliqué à moi au cours des 4 dernières semaines ...

	Pas du tout	Un peu	Beaucoup	Énormément
7. Je me suis isolé(e)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. J'ai négligé les personnes qui me sont proches	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. L'alcool a gâché ma relation avec mes proches	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Je me suis mal comporté(e) à l'égard des autres	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

S'est appliqué à moi au cours des 4 dernières semaines ...

	Pas du tout	Un peu	Beaucoup	Énormément
11. J'ai eu l'impression de passer à côté de ma vie de famille à cause de l'alcool	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. J'ai eu l'impression que les gens n'avaient pas confiance en moi	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. L'alcool a nui à ma vie sexuelle	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. L'alcool a nui à ma relation avec mes amis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Merci de tourner la page

Veillez vous rappeler de répondre seulement sur les 4 dernières semaines.

S'est appliqué à moi au cours des 4 dernières semaines ...

	Pas du tout	Un peu	Beaucoup	Énormément
15. J'ai eu du mal à être à jour dans mes papiers (comme mon courrier, organiser mes rendez-vous)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. L'alcool a nui aux conditions dans lesquels j'ai pu me loger (ex : changement de domicile, personne(s) avec qui je partage mon logement)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. Tout mon argent est passé dans l'alcool	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. J'ai eu des difficultés financières dues à l'alcool	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

S'est appliqué à moi au cours des 4 dernières semaines ...

	Pas du tout	Un peu	Beaucoup	Énormément
19. J'ai eu honte de moi-même	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. J'ai eu l'impression que les gens me méprisaient	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21. J'ai eu l'impression de gâcher ma vie	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22. Je me suis fait du souci de l'impact qu'a eu l'alcool sur ma santé	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
23. Je me suis fait du souci sur les problèmes que l'alcool a causé dans ma vie	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Merci de tourner la page

Veillez vous rappeler de répondre **seulement sur les 4 dernières semaines.**

S'est appliqué à moi au cours des 4 dernières semaines ...

	Pas du tout	Un peu	Beaucoup	Énormément
24. Je n'ai pas eu d'appétit	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
25. J'ai négligé mon apparence	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
26. J'ai négligé ma santé en général	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
27. Par ma faute je me suis trouvé(e) dans des situations risquées	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

S'est appliqué à moi au cours des 4 dernières semaines ...

	Pas du tout	Un peu	Beaucoup	Énormément
28. J'ai eu l'impression que rien n'a été plus important que l'alcool	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
29. L'alcool m'a contrôlé(e)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
30. Ma vie a tourné autour de l'alcool	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
31. J'ai planifié mes journées autour de l'alcool	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
32. J'ai eu l'impression de ne pas avoir le contrôle de moi-même	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Merci de tourner la page

Veillez vous rappeler de répondre seulement sur les 4 dernières semaines.

S'est appliqué à moi au cours des 4 dernières semaines ...

	Pas du tout	Un peu	Beaucoup	Énormément
33. Je n'ai pas eu de bonne nuit de sommeil	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
34. Je n'ai pas suffisamment dormi	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Merci d'avoir pris le temps de remplir ce questionnaire.

Veillez s'il vous plait retourner au début de ce questionnaire et contrôler que vous avez répondu à toutes les questions à chaque page.

Annexe 2: AQoLS version anglaise

Alcohol Quality of Life Scale (AQoLS)

Please read these instructions carefully

The purpose of this questionnaire is to find out how much alcohol has affected you **over the last 4 weeks**. Please do not answer for any longer than the last **4 weeks**.

"Alcohol" is used here to mean your general relationship with alcohol over the last 4 weeks, regardless of whether or not you have been drinking in this time period.

For **each** statement, please choose the response that best applies to you.

	Over the last 4 weeks this has applied to me ...			
	Not at all	A little	Quite a lot	Very much
1. I have felt I miss out on everyday activities with family and friends	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. It has been difficult for me to follow through on plans	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. I have been restricted in the places I can go because of alcohol	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. I have struggled doing physical activities due to alcohol (e.g. DIY, walking, cycling)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. It has been too much effort to do jobs around the house due to alcohol (e.g. cleaning, gardening, maintaining the house)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Alcohol has interfered with my ability to work	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please Turn Over

F-2

Please remember to answer for the **last 4 weeks only**.

	Over the last 4 weeks this has applied to me ...			
	Not at all	A little	Quite a lot	Very much
7. I have cut myself off from other people	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. I have neglected the people close to me	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Alcohol has damaged my close relationships	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. I have behaved badly towards other people	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	Over the last 4 weeks this has applied to me ...			
	Not at all	A little	Quite a lot	Very much
11. I have felt I miss out on family life because of alcohol	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. I have felt that people have no trust in me	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. Alcohol has interfered with my sex life	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. Alcohol has interfered with my relationships with friends	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please Turn Over

F-3

Please remember to answer for the **last 4 weeks only**.

	Over the last 4 weeks this has applied to me ...			
	Not at all	A little	Quite a lot	Very much
15. I have struggled to keep on top of my everyday household affairs (e.g. dealing with mail, organising appointments)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. Alcohol has had a negative effect on my housing situation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. All my money has gone on alcohol	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. Alcohol has caused me financial difficulties	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	Over the last 4 weeks this has applied to me ...			
	Not at all	A little	Quite a lot	Very much
19. I have felt ashamed of myself	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. I have felt that people look down on me	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21. I have felt that I am wasting my life	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22. I have worried about the effect alcohol has been having on my health	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
23. I have worried about alcohol causing problems in my life	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please Turn Over

F-4

Please remember to answer for the **last 4 weeks only**.

	Over the last 4 weeks this has applied to me ...			
	Not at all	A little	Quite a lot	Very much
24. I have had no appetite	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
25. I have neglected my appearance	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
26. I have neglected my general health	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
27. I have put myself in risky situations	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	Over the last 4 weeks this has applied to me ...			
	Not at all	A little	Quite a lot	Very much
28. I have felt that nothing matters more than alcohol	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
29. Alcohol has controlled me	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
30. My life has revolved around alcohol	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
31. I have planned my days around alcohol	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
32. I have felt as though I have not been in control of myself	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please Turn Over

F-5

Please remember to answer for the **last 4 weeks only**.

	Over the last 4 weeks this has applied to me...			
	Not at all	A little	Quite a lot	Very much
33. I have not had a good night's sleep	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
34. I have not been getting enough sleep	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Thank you for taking the time to fill in this questionnaire.

Please go back to the beginning and check that you have answered all the questions on each page.

Annexe 3: AQoLS version Japonaise

アルコール クオリティ・オブ・ライフ スケール (AQoLS)

指示をよく読んでください

本アンケートの目的は、過去4週間に、アルコールが及ぼした影響の程度を調べることです。過去4週間より前のことは回答しないでください。

ここでいう「アルコール」とは、過去4週間におけるアルコールとの全般的な関わりであって、その間飲酒していたかどうかは問いません。

各質問に対し、最も当てはまる回答を選んでください。

	過去4週間に当てはまる回答...			
	全くない	少し	かなり	非常に
1. 家族や友人との日常的な活動の機会を逸していると感じていた	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. 予定されていた計画を、最後までやり通すのは困難であった	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. アルコールのせいで、出かけられる場所が限られていた	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. アルコールのせいで、身体的な活動が困難であった (例：日曜大工、散歩、運動)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. アルコールのせいで、家の周りの事をするのに大変な努力を要していた (例：掃除、ガーデニング、家のメンテナンス)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. アルコールのせいで、仕事をする能力に支障が出ていた	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

裏返してください

過去4週間についてのみ回答してください。

	過去4週間に当てはまる回答...			
	全くない	少し	かなり	非常に
7. 他の人との繋がりを断ち切っていた	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. 親しい人をおろそかにしていた	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. アルコールのせいで、身内との人間関係が損なわれていた	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. 他の人に対して、ひどい態度を取ってしまった	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	過去4週間に当てはまる回答...			
	全くない	少し	かなり	非常に
11. アルコールのせいで、家庭生活の機会を逸していると感じていた	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. 人に信用されていないと感じていた	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. アルコールのせいで、性生活に支障が出ていた	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. アルコールのせいで、友人との関係に支障が出ていた	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

裏返してください

過去4週間についてのみの回答してください。

過去4週間に当てはまる回答...

全くない 少し かなり 非常に

15. 日常の家事を適切にこなし続けることが困難であった (例：郵便物の処理、請求への支払)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. アルコールのせいで、住宅事情に悪影響があった (例：立ち退き、実家に転居)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. 自分のお金を全て、アルコールに使ってしまった	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. アルコールのせいで、財政難に陥った	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

過去4週間に当てはまる回答...

全くない 少し かなり 非常に

19. 自分のことを恥ずかしく感じていた	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. 人に見下されていると感じていた	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21. 人生を無駄にしていると感じていた	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22. アルコールによる健康への影響が心配であった	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
23. 生活に問題を引き起こすアルコールのことが心配であった	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

裏返してください

過去4週間についてのみ回答してください。

	過去4週間に当てはまる回答...			
	全くない	少し	かなり	非常に
24. 食欲が無かった	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
25. 外見をおろそかにしていた	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
26. 自分の健康全般をおろそかにしていた	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
27. 危険な状況に身を置いていた（例：事故、けんか、法的トラブルに巻き込まれる）	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	過去4週間に当てはまる回答...			
	全くない	少し	かなり	非常に
28. アルコールよりも大事なことはないと感じていた	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
29. アルコールに支配されていた	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
30. 生活はアルコール中心に回っていた	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
31. アルコール中心に日々の計画を立ててきた	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
32. 自分をコントロールできていないと感じていた	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

裏返してください

過去4週間についてのみ回答してください。

	過去4週間に当てはまる回答...			
	全くない	少し	かなり	非常に
33. 夜良く眠ることができていなかった	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
34. 十分な時間睡眠が取れていなかった	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

アンケートにご協力いただきありがとうございます。

最初に戻って、各ページのすべての質問に回答していることを確認してください。

酒精生活质量问卷 (AQoLS)

请仔细阅读这些说明

此问卷的目的是了解在过去 4 周中，酒精对您产生了多大的影响。请您根据过去 **4** 周的情况回答问题。

“酒精”在这里指在过去 4 周中，酒精对您的一般影响，无论您在这段时间内是否喝过酒。

对于每个问题，请选择一个最适合您的答案。

在过去 **4** 周中，我的情况是.....

完全没有 一点 相当 非常大

1. 我感到我错过了与家人和朋友的常规活动	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. 我难以坚持完成预先制定的计划	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. 由于酒精，我可以去的地方受到了限制	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. 由于酒精，我从事体力活动有困难（例如，携带购物后的袋子、散步、骑车）	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. 由于酒精，我发现干家里的活太费精力了（例如，清洁、养花草、简单维护房屋工作如换灯泡）	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. 酒精影响了我的工作能力	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

请翻页

请记住只需回答过去4周的情况。

	在过去4周中，我的情况是.....			
	完全没有	一点	相当	非常大
7. 我把自己与其他人隔绝开来	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. 我忽视了我亲近的人	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. 酒精伤害了我与亲密的人之间的关系	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. 我对其他人的举止不好	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	在过去4周中，我的情况是.....			
	完全没有	一点	相当	非常大
11. 由于酒精，我感到自己错过了家庭生活	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. 我感到人们对我缺乏信心和信任	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. 酒精影响了我的性生活	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. 酒精影响了我与朋友的关系	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

请翻页

请记住只需回答过去4周的情况。

在过去4周中，我的情况是.....

完全没有 一点 相当 非常大

	完全没有	一点	相当	非常大
15. 我难以处理日常家庭事务（例如，去银行办理业务，安排预约）	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. 酒精对我的住房条件产生了负面影响	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. 我把所有的钱都花在酒精上了	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. 酒精导致了我经济困难	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

在过去4周中，我的情况是.....

完全没有 一点 相当 非常大

	完全没有	一点	相当	非常大
19. 我为自己感到惭愧	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. 我感到人们看不起我	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21. 我感到我在浪费生命	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22. 我担心酒精影响了我的健康	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
23. 我担心酒精正导致我的生活出现问题	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

请翻页

请记住只需回答过去4周的情况。

	在过去4周中，我的情况是.....			
	完全没有	一点	相当	非常大
24. 我没有食欲	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
25. 我忽视了我的外表	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
26. 我忽视了我的整体健康	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
27. 我将自己置于有风险的境地	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	在过去4周中，我的情况是.....			
	完全没有	一点	相当	非常大
28. 我感到没有什么比酒精更重要	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
29. 酒精控制了我的一切	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
30. 我的生活以酒精为中心	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
31. 我围绕着酒精计划一天的安排	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
32. 我感到我好像没有控制住自己	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

请翻页

请记住只需回答过去4周的情况。

	在过去4周中，我的情况是.....			
	完全没有	一点	相当	非常大
33. 我夜间睡眠不好	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
34. 我睡眠不足	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

感谢您花时间完成此问卷。

请返回开头处，检查您是否已经回答了每页上的所有问题。

술과 생활의 질 척도 (AQoLS)

다음 지시 사항을 자세히 읽으십시오

본 설문지의 목적은 **지난 4 주 동안** 술이 귀하에게 얼마나 영향을 주었는지 알아보는 것입니다. 지난 **4 주** 이전의 기간에 대해서는 답하지 마십시오.

본 설문지에서 사용하는 «술»이란 지난 4 주 동안 귀하의 음주 여부와 관계 없이 해당 기간 귀하와 술의 전반적인 관계를 뜻합니다.

각 질문에 대하여, 귀하에게 가장 많이 해당하는 응답을 고르십시오.

	각 질문에서 지난 4 주 동안 나에게 적용된 정도를 선택해 주십시오.			
	전혀 없음	약간	꽤 많음	매우 많음
1. 가족과 친구들과의 일상 활동에 참여하지 못했다고 느꼈다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. 계획대로 실천하기가 어려웠다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. 술 때문에 갈 수 있는 장소에 대한 제약이 있었다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. 술 때문에 육체적 활동(예: 쇼핑백 들고 가기, 걷기, 자전거 타기)을 하기가 힘에 겨웠다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. 술 때문에 집안 일(예: 청소, 정원 가꾸기, 집 수리 등)을 하기가 너무 힘이 들었다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. 술이 나의 업무 능력에 지장을 주었다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

페이지를 넘겨 주십시오.

지난 4 주에 한해서 응답하시는 것에 유의하여 주십시오.

	각 질문에서 지난 4 주 동안 나에게 적용된 정도를 선택해 주십시오.			
	전혀 없음	약간	꽤 많음	매우 많음
7. 다른 사람들과의 교제를 끊었다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. 나와 가까운 사람들에게 소홀했다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. 술은 나에게 특별한 의미가 있는 가까운 사람들과의 관계에 피해를 주었다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. 다른 사람들에게 나쁘게 행동했다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	각 질문에서 지난 4 주 동안 나에게 적용된 정도를 선택해 주십시오.			
	전혀 없음	약간	꽤 많음	매우 많음
11. 술 때문에 가정 생활에 참여를 못한다고 느꼈다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. 사람들이 나를 신뢰하지 않는다는 생각이 들었다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. 술이 성생활에 지장을 주었다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. 술이 친구들과의 관계에 방해가 되었다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

페이지를 넘겨 주십시오.

지난 4 주에 한해서 응답하시는 것에 유의하여 주십시오.

	각 질문에서 지난 4 주 동안 나에게 적용된 정도를 선택해 주십시오.			
	전혀 없음	약간	꽤 많음	매우 많음
15. 일상적인 집안 일(예: 우편물 관리, 약속 잡기 등)을 제대로 하는 것이 힘에 부쳤다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. 술은 나의 주택 사정에 부정적인 영향을 주었다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. 모든 돈을 술에 사용했다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. 술이 나에게 경제적 어려움을 초래했다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	각 질문에서 지난 4 주 동안 나에게 적용된 정도를 선택해 주십시오.			
	전혀 없음	약간	꽤 많음	매우 많음
19. 나 자신이 부끄럽다는 생각이 들었다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. 사람들이 나를 깔본다는 생각이 들었다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21. 내 인생을 낭비한다는 생각이 들었다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22. 술이 내 건강에 미치는 영향에 대해서 걱정을 했다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
23. 술이 내 인생에 초래하는 문제들에 대해 걱정했다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

페이지를 넘겨 주십시오.

지난 4 주에 한해서 응답하시는 것에 유의하여 주십시오.

	각 질문에서 지난 4 주 동안 나에게 적용된 정도를 선택해 주십시오.			
	전혀 없음	약간	꽤 많음	매우 많음
24. 식욕이 없었다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
25. 내 외모에 소홀히 했다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
26. 나의 전반적인 건강을 소홀히 했다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
27. 나 자신을 위험한 상황에 처하게 했다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	각 질문에서 지난 4 주 동안 나에게 적용된 정도를 선택해 주십시오.			
	전혀 없음	약간	꽤 많음	매우 많음
28. 술보다 더 중요한 것이 없다고 느꼈다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
29. 술이 나를 통제했다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
30. 내 삶은 술을 위주로 이뤄졌다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
31. 술을 위주로 하루 계획을 세웠다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
32. 내 자신을 통제하지 못하는 것처럼 느꼈다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

페이지를 넘겨 주십시오.

지난 4 주에 한해서 응답하시는 것에 유의하여 주십시오.

	각 질문에서 지난 4 주 동안 나에게 적용된 정도를 선택해 주십시오.			
	전혀 없음	약간	꽤 많음	매우 많음
33. 밤에 숙면을 취하지 못했다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
34. 잠을 충분히 잘 수 없었다.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

시간을 내어 설문지를 작성해주셔서 감사합니다.

각 페이지에 있는 모든 질문들에 응답하셨는지 처음부터 확인해 주십시오.

Annexe 6: enquête BDmiE: établissements participants et taux de réponse

Établissement	Participants (%)
Novancia	310 (25,8)
ICN	404 (20,2)
Mines Nantes	157 (28,5)
EBI	160 (22,7)
ENSAM	6400 (30,3)
UPsud	? (sur 29627)
U Bretagne Sud	? (sur 9000)
UPoitiers	1265 (15,8)
UMaine	717 (6,5)
U Strasbourg	247 (0,5)
UParis 6	1? (facebook)
UToulon	393 (4,3)
ESCOM	312 (49,6)
ENS rue d'Ulm	485 (20,2)
Mines St Etienne	144 (30,5)
ESSEC	480 (11,7)
UCergy	720 (4,5)
ULorraine	7100 (12,9)
Autres	2603

Annexe 7: AQoLS Version allemande

Alcohol Quality of Life Scale (AQoLS) - Deutsch

Bitte lesen Sie diese Anleitung sorgfältig durch!

Dieser Fragebogen soll herausfinden, wie sehr Sie **in den letzten vier Wochen** durch Alkohol beeinträchtigt wurden. Bitte denken Sie bei Ihren Antworten nur an **die letzten vier Wochen**.

Das Wort "Alkohol" meint hier Ihre generelle Einstellung zu Alkohol, unabhängig davon, ob Sie in den letzten 4 Wochen getrunken haben oder nicht.

Bitte markieren Sie bei **jeder** Aussage diejenige Antwort, die am besten auf Sie zutrifft.

In den letzten vier Wochen stimmte die Aussage ...

	überhaupt nicht	ein wenig	ziemlich	voll und ganz
1. Aus meiner Sicht sind alltägliche Aktivitäten mit meiner Familie und meinen Freunden zu kurz gekommen.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Ich hatte Schwierigkeiten das zu Ende zu bringen, was ich mir vorgenommen hatte.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Bestimmte Orte oder Plätze standen mir wegen des Alkohols nicht offen.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Ich hatte aufgrund von Alkohol Schwierigkeiten mit körperlichen Tätigkeiten (z.B. Heimwerken, Fahrradfahren, Spaziergehen).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Arbeiten rund ums Haus waren mir aufgrund von Alkohol zu anstrengend (z.B. Putzen, Gartenarbeit, Hausmeisterarbeiten).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Meine Arbeitsfähigkeit war durch Alkohol eingeschränkt.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Bitte umblättern

Bitte antworten Sie nur in Bezug auf die letzten vier Wochen.

In den letzten vier Wochen stimmte die
Aussage ...

	überhaupt nicht	ein wenig	ziemlich	voll und ganz
7. Ich habe mich von anderen Menschen abgekapselt.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Ich habe mir nahestehende Menschen vernachlässigt.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Alkohol hat Beziehungen zu mir nahestehenden Personen zerstört.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Ich habe mich zu anderen Leuten mies verhalten.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

In den letzten vier Wochen stimmte die
Aussage ...

	überhaupt nicht	ein wenig	ziemlich	voll und ganz
11. Wegen Alkohol habe ich in den letzten 4 Wochen kaum Familienleben gehabt.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. Andere Leute setzen anscheinend wenig Vertrauen auf mich.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. Alkohol hat mein Sexualleben beeinträchtigt.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. Alkohol hat meine Freundschaften beschädigt.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Bitte umblättern

Bitte antworten Sie nur in Bezug auf die letzten vier Wochen

In den letzten vier Wochen stimmte die
Aussage ...

überhaupt nicht ein wenig ziemlich voll und ganz

15. Es fiel mir schwer, meine Alltagsverpflichtungen zu erfüllen (z.B. Post erledigen, Termine absprechen).	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. Meine Wohnsituation hat sich durch Alkohol verschlechtert.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. Ich habe mein gesamtes Geld in Alkohol gesteckt.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. Ich hatte wegen Alkohol finanzielle Schwierigkeiten.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

In den letzten vier Wochen stimmte die
Aussage ...

überhaupt nicht ein wenig ziemlich voll und ganz

19. Ich habe mich vor mir selber geschämt.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. Ich hatte das Gefühl, dass Menschen auf mich herabsehen.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21. Ich hatte das Gefühl, dass ich mein Leben vergeude.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22. Ich habe mir Sorgen gemacht, dass Alkohol meine Gesundheit verschlechtert.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
23. Ich habe mir um all die Probleme wegen Alkohol Sorgen gemacht.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Bitte umblättern

Bitte antworten Sie nur in Bezug auf die letzten vier Wochen.

In den letzten vier Wochen stimmte die
Aussage ...

überhaupt nicht ein wenig ziemlich voll und ganz

24. Ich hatte keinen Appetit.

25. Ich habe mein Äußeres vernachlässigt.

26. Ich habe meine Gesundheit vernachlässigt.

27. Ich habe mich in riskante Situationen gebracht.

In den letzten vier Wochen stimmte die
Aussage ...

überhaupt nicht ein wenig ziemlich voll und ganz

28. Ich hatte das Gefühl, dass nichts so wichtig ist
wie Alkohol.

29. Alkohol hatte die Kontrolle über mich.

30. Mein Leben hat sich nur um Alkohol gedreht.

31. Ich habe meine Tage um den Alkohol herum
geplant.

32. Es war, als könnte ich mich nicht selber
kontrollieren.

Bitte umblättern

Bitte antworten Sie nur in Bezug auf die letzten vier Wochen.

In den letzten vier Wochen stimmte die
Aussage ...

	überhaupt nicht	ein wenig	ziemlich	voll und ganz
33. Ich hatte Schlafprobleme.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
34. Ich konnte nicht ausreichend schlafen.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Danke, dass Sie sich für's Ausfüllen die Zeit genommen haben!

**Bitte kontrollieren Sie noch einmal von ganz oben her, ob Sie auch alle Fragen
auf jeder Seite beantwortet haben.**

Annexe 8 : Liste des autres publications du candidat

Bonfils, N. A., Benyamina, A., Aubin, H. J., & Luquiens, A. (2015). Clozapine use for refractory impulse control disorders in Parkinson's disease: a case report. *Psychopharmacology (Berl)*.

Luquiens, A., Lourenco, N., Benyamina, A., & Aubin, H. J. (2015). Self-medication of achalasia with cannabis, complicated by a cannabis use disorder. *World J Gastroenterol* 21, 6381-3.

Aubin, H. J., Luquiens, A., & Berlin, I. (2014). Pharmacotherapy for smoking cessation: pharmacological principles and clinical practice. *Br J Clin Pharmacol* 77, 324-36.

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Reynaud, M., Luquiens, A., Aubin, H. J., Talon, C., & Bourgain, C. (2013). Quantitative damage-benefit evaluation of drug effects: major discrepancies between the general population, users and experts. *J Psychopharmacol* 27, 590-9.

Henry, C., Luquiens, A., Lancon, C., Sapin, H., Zins-Ritter, M., Gerard, S., Perrin, E., Falissard, B., & Lukasiewicz, M. (2013). Inhibition/activation in bipolar disorder: validation of the Multidimensional Assessment of Thymic States scale (MATHyS). *BMC Psychiatry* 13, 79.

Aubin, H. J., Luquiens, A., Bonnet, N., & Borgne, A. (2012). [From nicotine dependence to addictology]. *Rev Prat* 62, 356-9.

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Bellivier, F., Yon, L., Luquiens, A., Azorin, J. M., Bertsch, J., Gerard, S., Reed, C., & Lukasiewicz, M. (2011). Suicidal attempts in bipolar disorder: results from an observational study (EMBLEM). *Bipolar Disord* 13, 377-86.

Azorin, J. M., Luquiens, A., Aubrun, E., Reed, C., Gasquet, I., & Lukasiewicz, M. (2010). [Management of patients with acute manic or mixed episodes and outcome at three months]. *Encephale* 36, 226-35.