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Two decades of the Swiss program based on the prescription of Diacetylmorphine, from a public health intervention to a treatment option

Khan, Riaz ; Khazaal, Yasser ; Thorens, Gabriel ; Achab, S ; Annoni-Manghi, R ; Zullino, Daniele ;
Uchtenhagen, Ambros

Abstract: The medical prescription of diacetyl morphine (heroin) treatment is an addition to the therapeutic arsenal for patients gravely dependent or addicted to heroin use and for whom other forms of therapy have failed. In Switzerland, the Federal Office of Public Health SFOPH) has established directives and recommendations concerning prescription and administration of diacetyl- morphine.

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Synergy Between Canadian Practice and the World

Our Journal aims at displaying the creative aspects of Canadian Addiction practice. We contribute to a global pool of knowledge and in return we are informed by international experience. This issue provides excellent examples of this exchange.

Our clinical section reports on a number of topics of interest to Canadian Practitioners. The history of our field is replete with strategies enacted with the best intentions and resulting in unintended deleterious consequences. The current spike in Fentanyl street supply and the resulting victims have received widespread media coverage including the fact that many provinces are yet to enact remedial interventions. Efforts to rationalize the prescription of opioids may have resulted in a void promptly exploited by street suppliers. The article by Dr. Jafari et al reports on BC's experience and importantly provides recommendation for clinical prevention and management. Are there other policy lessons we must learn?

SBIRT has emerged as the promising strategy for primary care and emergency settings. Dr. Salvalaggio et al reports on such an intervention with physicians dealing with low socioeconomic populations and exposed to a training package compared to an unexposed group of physicians acting as control.

A heartening increase in levels of compliance and comfort with the strategy is elicited for up to one year following.

The third clinical contribution is based on a case report by Dr. Pedersen et al highlighting practical challenges in diagnosis and management of delirium tremens. This is one more reminder of the importance of recognizing signs and symptoms of alcohol withdrawal.

The international portion of this issue begins with an overview of two decades of the Swiss program involving the prescription of diacetylmorphine. This experience reported by Dr. Khan et al is widely recognized as a fine example of successful strategy based on individual tailoring and comprehensiveness.

Those of us who attended the successful ISAM meeting in Yokohama were treated to more than 150 presentations from some 40 countries. We have selected for you 36 abstracts picked for their possible relevance to Canadian practice and displaying the breadth and depth of this conference.

This fall the ISAM conference is in Dundee in October followed the following month by the CSAM conference in Banff. Great learning opportunities from both our proximal and more distant colleagues! Hoping you enjoy this issue.

Nady el-Guebaly, MD
Editor-in-Chief, CJA-JCA

Rising Fentanyl-related Overdose Deaths in British Columbia

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ABSTRACT:

There has been a surge in the number of fentanyl-detected overdoses in 2014 among people who use drugs in British Columbia. Provisional data indicates a constant increase in the number of fentanyl-detected overdoses over the past 3 years. A green pill, 'fake oxy' tablets, which resemble Oxycontin 80mg (oxycodone) have been found to contain variable amounts of fentanyl and not oxycodone. The physiological effects, symptoms and signs of fentanyl overdose are largely indistinguishable from that of heroin. This can complicate the management of overdoses in emergency settings. Emergency room physicians may find that the standard protocol dose of 0.4 – 0.8 mg of naloxone for heroin overdoses insufficient to reverse fentanyl overdoses. In such cases, in addition to investigations to rule out other potential use of other substances, larger doses of naloxone are often necessary to reverse the overdose. Take home naloxone programs are one harm reduction approach which is available in many jurisdictions in US¹ and was initiated in British Columbia in 2012 and it is currently available at 62 sites throughout the province of British Columbia.

Il y a eu une vague d'overdoses liées à la présence de fentanyl en 2014 parmi les personnes qui consomment des drogues en Colombie-Britannique. Des données

provisaires indiquent une augmentation constante du nombre d'overdoses liées au fentanyl au cours des trois dernières années. Des comprimés verts, « fake oxy », ressemblant à des comprimés d'Oxycontin 80mg (oxycodone), ont été identifiés comme contenant des quantités variables de fentanyl et non d'oxycodone. Les effets physiologiques, signes et symptômes d'une overdose par fentanyl s'apparentent à ceux de l'héroïne. Ce tableau complexifie la gestion des overdoses en situations d'urgence. Les médecins en salles d'urgence pourraient faire face à des situations où la dose standard de naloxone (0,4 – 0,8 mg) pour overdose d'héroïne soit insuffisante pour renverser les effets d'une overdose de fentanyl. Devant pareilles situations, en plus de chercher à éliminer la présence d'autres substances, de plus grandes doses de naloxone sont souvent nécessaires pour renverser l'overdose. Les programmes de naloxone à emporter sont une approche de réduction des méfaits disponible dans plusieurs juridictions aux États-Unis¹ et en Colombie-Britannique depuis 2012. Ils sont présentement disponibles dans 62 sites à travers la province.

There has been a surge in the number of fentanyl-detected overdoses in 2014 among people who use drugs in British Columbia. In the first 8 months of 2014 provisional data show a total of 49 fentanyl-detected deaths were identified compared to 51 in all of 2013 and 15 in 2012. Although most cases in 2014 were reported in the more populated lower mainland of BC (18 cases in Fraser health area) and 12 in metro Vancouver); cases were reported throughout BC². The BC Centre for Disease Control, Royal Canadian Mounted Police and Vancouver Police Department have sent out warnings to the public, people who use drugs and health care providers to raise awareness when overdoses have occurred³.

Increase in Fentanyl-related death has been previously reported in the US. During the summer of 2005, multiple cities in the United States began to report outbreaks of fentanyl-associated fatalities among illicit drug users. Schumann et al⁴ reviewed the Cook County medical examiner findings for the 18 month period from April 1st 2005 to December 31st 2006 and identified 342 illicit fentanyl-related fatalities occurring during the study period. Fentanyl-related deaths rose dramatically between April and July 2006. Approximately 84% of the cases were men, 50.6% involved black men and most victims (70.8%) resided in the city of Chicago. In a similar study⁵ reported a surge in the number of fentanyl-related death in Wayne County between the period of July 2005 and May 2006.

Fentanyl is a controlled substance classified as a schedule I substance⁶ in Canada and schedule II in the United States⁷ due to its high potential for abuse. Prescribed fentanyl is a potent synthetic opioid-analgesic which is up to 100 times more potent than morphine⁸. It is indicated and prescribed to treat severe, often chronic, pain such as that experienced by cancer patients. Exposure to fentanyl can occur from a variety of sources. A green pill (marked OXY 80) obtained through the illicit market has become readily available across Canada. However the 'fake oxy' tablets which resemble Oxycontin 80mg (oxycodone) have been found to contain variable amounts of fentanyl and not oxycodone⁹. In a second group, heroin users may be exposed to fentanyl laced heroin or powder containing no heroin¹⁰. These two groups may not be aware of the risk of exposure to an opioid which is more potent than realized. A third group may purposefully seek out fentanyl as their drug of choice over other opioids. These users obtain fentanyl from either illegally produced or from pharmaceutical sources. Fentanyl patches have been diverted by pharmacy theft, fraudulent prescriptions and illicit distribution.

The physiological effects, symptoms and signs of fentanyl overdose are largely indistinguishable from that of heroin. This can complicate the management of overdoses in emergency settings.

Fentanyl may produce more prolonged respiratory depression than other opioid analgesics. Hess et al¹¹ found a rapid decrease in plasma levels of fentanyl following intravenous injection in the first 20 minutes, however, the level of fentanyl and its metabolites rose smoothly, stayed at higher levels until about 3 hours, and then declined. Such observation suggests that the fentanyl metabolites have pharmacological properties similar to long acting opioids such as methadone.

The amount of naloxone needed to counteract opioid overdose depends on a number of factors such as the dose of the opioid used and its half-life. Emergency room physicians may find that the standard protocol dose of 0.4 – 0.8 mg of naloxone for heroin overdoses insufficient to reverse fentanyl overdoses¹². In such cases, in addition to investigations to rule out other potential substances, larger doses of naloxone are often necessary to reverse the overdose¹³. An initial dose of 0.4 mg to 2 mg of naloxone can be given and if no response observed within 2-3 minutes additional doses of naloxone to a maximum of 10 mg can be administered¹⁴.

The pharmacodynamics actions of naloxone lasts for a period of 60 to 90 minutes¹⁵ which results in rapid redistribution away from the brain. This can result in patient renarcotising, sedation and overdose if they are discharged early from medical care. It is recommended that all patients to be monitored for the signs and symptoms of re-sedation for at least 4 hours from the last dose of naloxone administration, however patients overdosed on long-acting opioids should be monitored longer¹⁵. This is of particular importance to those who have received naloxone in the community by a friend or a family member. In these individuals an observation period in a hospital is recommended.

People who self-administer OXY 80 tablets often believe they are consuming oxycodone and not fentanyl. This misconception may complicate their treatment in the emergency room, in detox, or in treatment settings. Currently available point-of-care urine drug tests typically test for opioids such as morphine, heroin and oxycodone but do not specifically test for fentanyl. Unless fentanyl is tested for specifically, the opioid tests will appear negative leading to potential misinterpretation and not managed appropriately. Fortunately, many manufacturers now sell separate tests for fentanyl. Testing is recommended throughout the treatment journey, from detection to ongoing monitoring. Because differentiation of the opioid causing overdose based on clinical presentation is challenging we recommend emergency rooms, detox services and community care clinics to adopt appropriate urine drug testing kits which have the capability of detecting both common and emerging drugs. Emergency services should also be familiar with the protocols for administration of the naloxone in such complicated cases.

It is important to note that illicit market for substances is a dynamic process and drugs emerge or re-emerge. From our experience within Vancouver Coastal Health addiction services, laboratory confirmatory results of opioid positive urines in some self-reported heroin users may contain no heroin metabolites. Instead, fake fentanyl which is produced in underground labs or imported to North America is being sold as heroin. Other sources of fentanyl are diversion within the health care facilities¹⁶, stolen from pharmacies¹⁷ or diversion by patients. Awareness of the potential risks of prescribing medications of potential abuse, and to screen and monitor such clients for potential risks of abuse or diversion and taking

any necessary action⁸. In the situation in which a highly potent product like fentanyl appears and is being sold as heroin can translate into potentially lethal overdoses.

Take home naloxone programs are one harm reduction approach which is available in many jurisdictions in US¹ and was initiated in British Columbia in 2012¹⁹. THN is currently available at 62 sites throughout the province of British Columbia. BC Centre for Disease Control has sent out a message to the community and advised drug user:

- Be aware illicit drugs are of unknown constituents and concentration and may contain fentanyl
- Don't use alone
- Taste a small amount of the drug first
- Don't mix drugs and don't use alcohol too
- Use InSite if possible [for Vancouver]
- Make a plan/know how to respond in case of OD
- Carry naloxone

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- Call 911 right away if someone ODs

Regular sampling of the street opioids and content analysis that provides updates to care providers and emergency room services would provide an opportunity for ongoing monitoring of the potential causes of the overdose and provision of proper preventive measures such as media briefs, posting warning signs in clinics, pharmacies, community and harm reduction centers. In order to address the rise in number of fentanyl and other opioid overdose deaths, a collaborative environment between laboratories, police, community organizations that deliver services to substance users, emergency response team, emergency room staff, medical clinics, and jail and prison program is needed to prevent overdose deaths among substance users. In British Columbia, a Fentanyl campaign called "Know Your Source" was launched on March 2015 to raise the awareness within the communities.

Effect of a Knowledge Translation Intervention on Physician Screening, Brief Intervention, and Referral to Treatment Behaviour in a Socioeconomically Disadvantaged Setting

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ABSTRACT

Objectives: Screening, Brief Intervention and Referral to Treatment (SBIRT) is an effective but under-utilized approach for managing alcohol and drug misuse in primary care and emergency settings. Implementing SBIRT with low socioeconomic position patients also requires attention to patient engagement. This study evaluated the impact of a knowledge translation intervention on physician SBIRT behaviour.

Methods: A nonrandomized, two-group, pre-post, quasi-experimental intervention design was used. Primary care and emergency physicians working with disadvantaged populations in a Canadian city were geographically allocated to control or intervention groups. Intervention

physicians were offered a suite of activities including didactic sessions, electronic modules, point-of-care resources, and access to local champions. The primary outcome was physicians' self-reported SBIRT practices. Chi-square and ANOVA analyses compared intervention and control groups and assessed for participation effects. Subsequent regression analyses adjusted for confounding baseline characteristics.

Results: 131 physicians (78 intervention and 53 control) participated; 64 (49%) completed all follow up measures. Resources were well received, with uptake ranging from 25% (e-modules) to 63% (point of care resources). After adjusting for demographics, baseline comfort level, and baseline SBIRT behaviour, the intervention was associated with an increase in SBIRT behaviour at 12 months. This effect was mediated by an increase in physician comfort working with the target population.

Conclusions: A SBIRT knowledge translation intervention for physicians working with low-socioeconomically positioned patients was associated with an increase in comfort level, which in turn mediated an increase in physician-reported SBIRT behaviour.

Objectifs: Dépistage de l'abus d'alcool, intervention rapide et orientation (DIRO) est une approche efficace mais peu utilisée en contexte de soins de santé primaires et d'urgence pour la gestion de l'abus d'alcool et de drogues. Le processus d'implantation de DIRO auprès de patients à statut socioéconomique faible doit également tenir compte de l'engagement des patients. Cette étude a évalué, parmi des médecins, l'impact d'une intervention de transfert de connaissances sur les comportements en lien avec l'approche DIRO.

Méthodologie: L'intervention a respecté un devis quasi-expérimental, pré-post, de deux groupes répartis de façon non aléatoire. Des médecins qui travaillent en milieu de soins primaires et à l'urgence auprès de populations défavorisées d'une ville canadienne ont été géographiquement répartis dans un groupe contrôle ou expérimental. Les médecins du groupe expérimental se

sont vus offrir des activités telles que des séances didactiques, des modules électroniques, des ressources au point de service et un accès aux champions locaux. Le principal résultat d'intérêt était les pratiques DIRO auto-rapportées. Des analyses de la variance (ANOVA) et khi carré ont été réalisées pour comparer le groupe expérimental avec le groupe contrôle et évaluer les effets de la participation. Les analyses de régression subséquentes ont permis l'ajustement relatif aux facteurs confusionnels mesurés au début.

Résultats: 131 médecins (78 dans le groupe expérimental et 53 dans le groupe contrôle) ont participé; 64 (49% ont complété toutes les mesures au temps de suivi). Les ressources offertes ont été bien accueillies; le taux de participation aux modules électroniques était de 25% et celui pour les ressources au point de service de 63%. Après l'ajustement pour les données démographiques, le niveau de confort initial et les comportements DIRO initiaux, l'intervention est associée à une augmentation des comportements DIRO après 12 mois. Cet effet est facilité par un plus grand confort de la part des médecins à travailler avec des populations défavorisées.

Conclusion: Une intervention de transfert de connaissances sur l'approche DIRO auprès des médecins travaillant avec des patients à statut socioéconomique faible est associée à un plus grand confort des médecins qui, à son tour, favorise la pratique de l'approche DIRO tel qu'auto-rapportée par les médecins.

INTRODUCTION

Alcohol and drug use disorders are associated with substantial individual morbidity and public cost^{1,2,3,4,5}. Upwards of 15% of adults engage in hazardous drinking and drug use and are at risk of progressing to a severe substance use disorder (SUD)^{1,2}. The Screening, Brief Intervention, and Referral for Treatment (SBIRT) approach incorporates validated screening instruments, brief counseling using principles of motivational interviewing, and referral to more intensive treatment for individuals with a moderate-to-severe SUD⁶. Brief intervention has been recommended for use in both primary care and emergency care settings^{7,8,9} as it reduces overall consumption and harmful behaviours associated with non-dependent substance use^{10,11}. Although brief intervention by itself may be insufficient to effect behaviour change in people who present to primary care or emergency department settings and meet the criteria for a more severe SUD¹², it is a logical first step in connecting patients with more specialized treatment approaches.

Despite its potential to improve health outcomes, SBIRT has not been uniformly adopted in clinical practice, and is only partially implemented in many practice settings that

have committed to its adoption^{13,14}. Health care providers (HCPs) frequently cite insufficient addiction medicine training, time to conduct assessment, and practice resources to support this intervention approach^{15,16}. Other clinical and social problems may hold higher priority for both patients and their care teams¹⁷. Care teams may also be concerned about inadequate reimbursement and net financial cost associated with implementation. In addition, the beliefs, ideologies, and interests HCPs hold about addictive behaviours and their management need to be understood and addressed in any SBIRT implementation strategy¹⁸. Further, for groups traditionally occupying a low socioeconomic position (SEP), meaningful engagement in their care is essential to their adoption of healthy behaviours recommended by HCPs¹⁹. Individuals living with unstable housing, poverty, or other disadvantage are accustomed to discordant interpersonal styles, discrimination, financial and administrative obstacles, physically impractical advice, and inadequate social work resources in health care settings; these experiences contribute to reduced uptake and impact of evidence-based health care interventions^{20,21,22,23}.

OBJECTIVES

SBIRT implementation requires a multipronged strategy which effectively addresses these barriers to implementation and considers the health and psychosocial needs of the population being served. We developed a suite of knowledge translation (KT) resources designed to enhance uptake of SBIRT in socioeconomically disadvantaged practice settings; the objective of this study was to determine whether this KT strategy contributed to a change in self-reported physician use of SBIRT.

METHODS

OVERVIEW

The physician KT strategy was implemented and evaluated in Edmonton, Canada as part of a larger project which also included a health navigation KT strategy for low SEP patients. A nonrandomized, two-group, pretest-posttest, quasi-experimental intervention design was used for the evaluation; our study protocol has been previously described²⁴. An iterative approach to KT was used²⁵, whereby literature syntheses, pre-implementation needs assessments, the identification of content champions in participating practice settings, and patient and clinician involvement contributed to the development and refinement of the KT strategy before, during, and after implementation. The research team endorsed principles of Community Based Participatory Research (CBPR) to ensure that inner city community members and key

health and social service organizations serving this community were active participants in resource development, implementation, and evaluation^{26,27}. The study received approval from the local Health Research Ethics Board prior to protocol implementation.

SAMPLE

Physician members of Edmonton-area Primary Care Networks (PCNs), Emergency Departments (EDs), and generalist residency training programs serving low SEP Edmonton neighbourhoods were invited to participate in the study via multiple mail-outs, newsletters, and meeting announcements. Consenting members of two PCNs, two EDs, and two residency programs were allocated by geographic practice location to receive the KT intervention after enrolment. Physician members from a third PCN, ED, and residency program were allocated to the control condition; control group participants received no targeted KT during the study period but were able to access KT resources upon completion of the study.

PROCEDURES

Physicians indicated their consent to participate by completing and returning the paper or electronic version of a baseline survey assessing demographics, SBIRT use, comfort level, and attitudes. The first six months of the study period focused on patient-level KT implementation; to ensure stability of physician characteristics over this initial time period, a repeat survey was administered six months following enrolment. Over the following six months, intervention group physicians were invited to access the developed KT resources. All physician participants were subsequently asked to complete a 12 month follow-up survey; in this latter survey, data were also collected on resource uptake and usefulness.

INTERVENTION

The KT resources were implemented over a six month period. Physicians and their multidisciplinary colleagues were initially invited to attend a two-to-three hour workshop incorporating didactic information on SBIRT and patient engagement, video demonstrations, facilitated small group SBIRT skills practice, and a discussion of implementation challenges and solutions. Community members with lived addiction experience were available at a number of the sessions to answer questions and discuss scenarios with the participants. Workshop format and timing varied according to the needs of the study site,

with at least one workshop being offered on site at each PCN and ED during a time slot typically associated with continuous professional learning. Workshop content was also available in webinar and podcast formats. Participants were also given the opportunity to join a physical tour of inner city service locations. Print point-of-care tools including a patient-oriented health navigation booklet, SBIRT pocket cards, implementation tip sheets, and local referral resource lists were distributed. These, along with two electronic case-based learning modules and links to other available online resources, were uploaded to a web platform to facilitate ongoing resource access. A physician and a multidisciplinary team member identified as champions within each PCN and ED assisted with workshop facilitation for their study site and were available for later on site implementation support.

MEASURES

Baseline demographic variables were collected to characterize participants by age, gender, years of experience, discipline (family vs. emergency medicine), and practice status (resident vs. licensed practicing physician). Pre- and post-intervention self-report data were collected on perceived comfort level working with the target population, as well as attitudes (Short Understanding of Substance Abuse Scale (SUSS)²⁸, Attitudes Toward Injecting Drug Users scale (ATIDU)²⁹, Health Professionals Attitudes Toward the Homeless Inventory (HPATHI)³⁰); both comfort level and attitudes were hypothesized a priori to be potential influences on SBIRT use²⁴. For practice behaviours, physicians self-reported the frequency with which they performed SUD screening, brief intervention, referral to SUD services, and in-clinic follow-up for SUDs.

Examination of baseline comfort levels demonstrated high inter-correlations among the four comfort self-report items (comfort managing addiction, comfort managing low SEP patients, success in finding common ground with patients with addiction, success in finding common ground with low SEP patients). Internal consistency of a composite scale reflecting physicians' comfort and success working with the target patient population was good ($\alpha=.81$). This new composite measure was used in subsequent regression analyses.

ANALYSES

First, descriptive analyses were undertaken to examine

the distribution for each variable within and between intervention groups and describe correlations between covariates. Next, bivariate chi-square and ANOVA analyses were conducted to determine whether the intervention and control groups were equivalent on study covariates and physician SBIRT behaviour at baseline. Next we used analysis of partial variance (APV³¹) to determine whether changes in physician SBIRT behaviour occurred over the follow-up period, and if so, whether changes in these outcomes related to intervention vs. control conditions and baseline study covariates. In APV, covariates are entered into a regression equation, followed by sets of independent variables. When the dependent variable is a post-intervention score and the pre-intervention

score is used as a covariate, APV may be used to predict residual change scores, i.e., change from baseline to follow-up, adjusted for participants' pre-intervention scores. Baseline scores on each outcome variable were entered in the first step of each analysis. Step 2 entered demographic covariates. Step 3 entered a variable carrying the research design, (i.e., study condition, dummy-coded as 0 = controls; 1 = intervention). Finally, when a significant effect of the KT intervention was observed in the APV analysis, we conducted mediational analyses to determine whether physicians' self reported level of comfort working with the target population mediated the association between exposure to the intervention and change in the outcome variable.

RESULTS

BASELINE CHARACTERISTICS

131 physicians (78 intervention and 52 control) agreed to participate in the project and completed the baseline assessment. There was some loss to follow-up at the 6 and 12 month assessments, with 82 physicians (63%) responding to the six-month survey and 64 physicians (49%) responding to the 12-month survey (Figure 1). Study participation relied on the voluntary return of baseline and follow-up surveys, and reasons for refusal and loss to follow up could not be tracked; however, rates of recruitment and attrition were similar in both the intervention and control arms. Physicians returning a 12-month survey (administered after intervention) were included in our analyses.

Participant age, gender, experience, discipline, and practice status were similarly distributed in the intervention and control groups (Table 1). Baseline self-reported SBIRT use was also comparable. The intervention group held more positive baseline attitudes towards people who inject drugs and also cited a higher baseline level of comfort managing addiction than their control group counterparts; these differences were accounted for in subsequent analyses.

Figure 1. Participant flow diagram

TABLE 1. BASELINE CHARACTERISTICS BY INTERVENTION STATUS

Variable	Intervention (n=78)	Control (n=53)	Total	p
Mean Age	37(10.2)	38(12.8)	38(11.3)	ns
Female Gender	30(39%)	23(43%)	53(41%)	ns
Years Since Graduation	12(9.3)	13(12.5)	12(10.8)	ns
Residency Completion	51(67%)	36(68%)	87(67%)	ns
FM Discipline	30(39%)	20(38%)	50(38%)	ns

RESOURCE UPTAKE AND USEFULNESS

Intervention physicians who opted to provide resource feedback reported resource uptake ranging from 25% for electronic modules to 63% for point-of-care reminders (Table 2). 50-100% of respondents who used each resource found the specific resource to be useful in practice. Resources involving human interaction or narratives (e.g. workshops, champions, video vignettes) were ranked more highly. Over 80 comments were provided, some noting that the resources were clinically useful and easy to access, whereas others cited lack of time, other priorities, or incomplete awareness of the available resources. Similar comments were received for each individual resource.

TABLE 2. RESOURCE UPTAKE AND USEFULNESS

Resource	Number of participants reporting resource use (%)	Number of participants ranking used resource as “useful” or “very useful” (%)
Presentations	20(53)	20(100)
Videos	18(47)	14(78)
E-modules	4(25)	2(50)
Champions	15(42)	13(87)
Inner City Tour	11(30)	8(73)
Point-of-care Reminders	24(63)	16(67)
Web Resources	17(45)	14(82)

SBIRT BEHAVIOUR

First, existing influences on SBIRT practice behaviour were examined at baseline. Female gender, licensed physicians, increasing years of practice, and higher baseline comfort predicted a higher baseline frequency of screening behaviour. Family medicine discipline and higher baseline comfort predicted a higher baseline frequency of brief intervention behaviour. Gender, family medicine discipline, and higher baseline comfort predicted a higher baseline frequency of addiction referral behaviour.

Using conservative, within-subjects regression analyses that (a) adjusted for physicians' own baseline brief intervention behavior ($\Delta R^2 = .07$ [$\Delta F(1,46) = 4.29$], $p < .04$; $\beta = .29$), and (b) adjusted for potential confounding effects of age ($\beta = -.12$), gender ($\beta = -.02$), years of practice ($\beta = -.26$), and medical discipline ($\beta = .20$) ($\Delta R^2 = .21$ [$\Delta F(5,41) = 2.43$], $p < .05$), exposure to the KT intervention predicted post-KT brief intervention behaviour ($\Delta R^2 = .06$ [$\Delta F(1,40) = 3.98$], $p < .05$; $\beta = .28$), but not screening or referral behaviour.

COMFORT AS A MEDIATOR OF SBIRT BEHAVIOUR

A supplemental mediational analysis was performed to determine whether the intervention-assisted increase in self-reported use of brief intervention was influenced by changes in self-reported comfort³². Exposure to any amount of the intervention was positively associated with subsequent use of brief intervention. Regression analysis confirmed that exposure to intervention was positively associated with 12 month ratings of comfort ($\beta = .37$, $p < .004$). After statistically controlling for changes in self-reported comfort levels at 12 months, exposure to the intervention no longer significantly predicted the outcome variable ($\beta = .08$, ns). Results of the mediational analysis provide evidence that intervention-assisted increases in self-reported use of brief intervention were mediated by changes in physicians' self-reported ratings of comfort and success working with the target population.

EFFECTS OF STUDY PARTICIPATION

Some overall study participation effects were also observed during preliminary ANOVA analyses (Table 3). Independent of their intervention condition, participants in general reported higher screening and addiction referral behaviour post-intervention. Participant attitudes also changed globally in a favourable direction, with higher Psychological Model of Addiction and lower Disease Model of Addiction scores on the SUSS post-intervention.

TABLE 3. CHANGES IN SELF-REPORTED ATTITUDES AND SBIRT BEHAVIOUR ACROSS TOTAL PARTICIPANT SAMPLE, INDEPENDENT OF INTERVENTION STATUS

Behaviour*	Pre (n=129)	Post (n=63)	Testing Effect
SUD Screening	3.3(0.57)	3.6(0.76)	sig 0.008
Brief Intervention	3.3(0.81)	3.5(0.91)	ns
Referral for Treatment	2.9(0.96)	3.3(0.78)	sig 0.017
Post-Treatment Follow-up	3.5(1.08)	3.4(0.95)	ns
SUSS Subscale	Pre (n=129)	Post (n=52)	Testing Effect
Psychological Model**	19(2.7)	15(2.2)	sig 0.00
Disease Model†	18(5.4)	10(3.1)	sig 0.00
Eclectic Orientation Model‡	22(3.2)	22(4.0)	ns

*Asked on a five point scale from None of the Time (1) to All of the Time (5)

**Higher scores indicate a belief that alcoholism is a learned behavior shaped by cultural influences and family environment

†Higher scores on this scale indicate a belief that alcoholism is a progressive, incurable disease that can only be arrested by abstinence

‡Higher scores indicate a belief that alcoholic clients are diverse individuals who require different treatment approaches

INTERPRETATION

Despite the effectiveness of SBIRT in research settings, real world implementation of this counseling strategy has proven challenging. Patient engagement is an additional challenge to SBIRT implementation in underserved practice settings. Our data suggest that a suite of portable, practice-based KT resources for patient-engaged SBIRT provides a modest contribution to physician behaviour change, in particular counseling maneuvers requiring enhanced knowledge and skills practice (i.e. brief intervention). Further, it is feasible to adhere to CBPR principles and implement KT strategies like these in an underserved practice setting.

For this intervention effect to be enhanced and sustained over the longer term, KT strategies must remain intensive and well resourced, with committed decision makers, dedicated personnel, change management support, and the modest budgets and infrastructure required to support SBIRT initiatives. Enablers of SBIRT behaviour warrant further exploration as a potentially cost effective means to enhance SBIRT behaviour change. Though some influences on physician SBIRT behaviour (gender, discipline, experience) are fixed and have traditionally been associated with a higher provision of screening and counseling maneuvers³³, others, such as comfort level, may be amenable to change. Unfortunately, learner attitudes towards marginalized populations have been shown to decrease over the course of medical training, underscoring the urgent need for effective interventions in this area³⁴.

The presence of study participation effects independent of exposure to the KT intervention mirrors other studies evaluating the impact of SBIRT on alcohol use by patients, in which the baseline screening questions themselves contribute to a reduction in high risk consumption

with or without an associated brief intervention³⁵. In the case of our study physicians, it is plausible that responding to questions about practice behaviour and addiction attitudes heightened awareness of these issues in practice, and that a more complex KT intervention was not required to remind physicians to ask their patients about alcohol and drug use. Further KT activities targeted to general awareness about addiction may be ideal to support a change in screening behaviour, prior to the introduction of more comprehensive KT activities designed to increase physician comfort with subsequent counseling maneuvers (i.e. brief intervention).

LIMITATIONS

The KT strategy used in this study introduced several supports in tandem; evaluation of the effects of all resources combined did not permit the identification of the most effective supports among them. The combined approach to implementation and evaluation was deliberate, as it has been shown that single KT interventions are minimally effective and multipronged approaches are needed³⁶.

Physician recruitment and retention into the study was challenging despite the identification of local champions, multiple recruitment means, and repeated communication with participants using their preferred contact medium. Recruitment beyond participating EDs and PCNs was not feasible, as local low SEP populations were concentrated most heavily in the participating geographic areas. Physicians who chose not to participate may have felt that SBIRT was not a priority, and as a result, would have likely had differing baseline characteristics and experienced different behaviour changes as a result of participation. The existing sample may also be underpowered to detect larger intervention effects. We note that attrition rates were similar in both intervention and control groups, suggesting that effects observed are accurate.

Additional limitations include our inability to assess fidelity to SBIRT and actual practice behaviour due to a lack of available tools to perform these assessments. We were also unable to identify a reliable pool from which to independently recruit non-physician health care team members, who play an increasingly prominent role within primary and emergency care teams; it is possible the behaviour of these multidisciplinary team members differs from, or influences, that of their physician colleagues, and vice versa. Further, linking physician use of SBIRT directly to patient behaviour change (i.e. reduced consumption, risk taking, addiction treatment, etc.) was not possible for ethical reasons; physician-patient linkage carried unacceptable patient privacy risks for data custodians. These limitations certainly warrant further exploration and would be a valuable contribution to our understanding of optimal SBIRT implementation.

CONCLUSION

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The Challenge of Differentiating Delirium Tremens from Other Causes of Delirium in Hospitalized Patients: A Case Report & Review of the Challenge

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ABSTRACT

Alcohol withdrawal is a common presentation in patients with alcohol use disorder. If severe, alcohol withdrawal may present as delirium tremens (DT) characterized by confusion, agitation, disorientation and hallucinations, occurring approximately 48 hours after cessation of alcohol. Delirium tremens is associated with significant morbidity and mortality. Thus, it is important for clinicians to know how to diagnose and treat delirium tremens. We report on a case of delirium in a patient with a history of alcohol withdrawal in which there was a clinical question regarding the etiology of the delirium. Challenges in diagnosis and management of delirium tremens are discussed.

Les symptômes de sevrage alcoolique sont fréquents chez les patients avec des troubles de consommation d'alcool. Un sevrage sévère peut être accompagné d'un délire alcoolique aigu, aussi appelé delirium tremens (DT), qui se caractérise par de la confusion, de l'agitation, de la désorientation et des hallucinations et qui apparaît environ 48 heures suivant la dernière consommation. Le DT est associé à une morbidité et une mortalité plus importante. Il est donc important que les cliniciens sachent comment diagnostiquer et traiter le DT. Nous faisons rapport d'un

cas de delirium chez un patient avec des antécédents de sevrage alcoolique et chez qui la cause du delirium suscitait des questions d'ordre clinique. Les difficultés liées au diagnostic et à la gestion du DT sont discutées.

INTRODUCTION

Alcohol use disorder (AUD) is common worldwide and accounts for major morbidity and mortality globally¹. In Canada, the age-standardized prevalence of AUD has been estimated to be approximately 7% in recent years, with some developed nations reporting rates as high as 19%². Rates of emergency department visits and hospital admissions attributable to AUD are high in many jurisdictions³⁻⁵.

Alcohol withdrawal is a common hospital presentation in patients with AUD. The clinical presentation of alcohol withdrawal (Table 1) commonly includes autonomic hyperactivity manifesting as tachycardia, hypertension, tremor and/or diaphoresis. In severe cases it can be associated with delirium tremens (DT), which presents with confusion, agitation, disorientation, hallucinations and is classically accompanied by an autonomic storm⁶. DT typically starts 48-96 hours after cessation or reduction of alcohol intake, peaking 1-2 days after onset, can last several weeks, and has been estimated to occur in 5-25% of patients with alcohol withdrawal symptoms⁷⁻⁸, and has been associated with a mortality rate of up to 8% in untreated patients⁷.

In patients presenting to hospital with acute illness, it can be challenging to differentiate DT from delirium due to other causes (e.g. infection). Moreover, since alcohol withdrawal is commonly treated with benzodiazepines, which can cause delirium, the differential diagnosis of DT can be particularly challenging. Knowing how to clinically differentiate causes of delirium, and treat delirium empirically in the face of uncertainty, is important and has implications for healthcare resources (e.g. length of stay) and patient outcomes⁹. This case report describes a real case of delirium in a patient in alcohol withdrawal and highlights the clinical challenges inherent in this presentation.

CASE REPORT

A 65 year old male with a history of severe alcohol use disorder including alcohol-related seizures presented to the emergency department of an inner-city hospital in Vancouver, Canada, on November 11, 2013 after a fall. On first nursing assessment, the patient reported having consumed between 5-8 beers at home the same night. The patient was oriented to person and place, but not time. His thoughts and speech were clear. His gait was unstable. His blood pressure was 143/67, heart rate 110 and respiratory rate 16. He maintained his own airway and breathing was noted to be even and unlaboured.

The electrocardiogram (ECG) showed tachycardia with regular heart rhythm. His skin was warm and dry. Laboratory values included a blood alcohol level of 72 mmol/L, elevations of aspartate transaminase (AST) and gamma-glutamyl transpeptidase (GGT) to 65 and 62 U/L respectively, reduced albumin of 26 g/L and an elevated international normalized ratio (INR) of 1.3. Alanine Aminotransferase (ALT) was normal at 29 U/L. Sodium, potassium and chloride were 145 mmol/L, 4.4 mmol/L and 116 mmol/L respectively. Computed Tomography (CT) scan of the patient's head showed no acute head injury. The patient was diagnosed as having acute alcohol intoxication and associated fall and given 2 L normal saline, magnesium sulfate 2 g IV, thiamine 100 mg and multivitamins. Over the next several of hours, the patient was asleep in the emergency department and was noted to be responsive to verbal stimuli.

Further assessment revealed a recent alcohol consumption history of 30 beers/day and a history of alcohol-related seizures. He also reported smoking half-a-pack of cigarettes per day and a 50 pack-year history of cigarette smoking, but denied any recreational drug use.

Further exam noted that the patient looked unwell, had tremor and was confused. Vital signs on the ward on November 11 as well as subsequent dates are reported in Table 2. Heart rate ranged from 60-110 and blood pressure ranged from 110-143/51-77 that day. The Clinical Institute Withdrawal Assessment for Alcohol (CIWA) protocol was initiated (scores ranged from 11-12 that day) and the patient received 1 mg of lorazepam PO at 21:55 and again at 23:15.

The hospital's addiction consultation service was consulted, and saw the patient on November 12. Because he had a history of alcohol related seizures, the patient was given diazepam 10 mg PO BID. He had CIWA scores ranging between 6 to 11, and received 1 mg doses of lorazepam PO at 08:35 and also once in the afternoon due to CIWA scores greater than 9. That day, a chest x-ray showed

pleural fluid on the right chest wall and airspace consolidation in the right middle and lower lungs, pneumonia was diagnosed and treatment with Ceftriaxone ordered for 5 days.

On November 13, heart rate was 102-118 and CIWA scores ranged from 8 to 18. The patient received 14 mg of lorazepam (5 x 2 mg and 4 x 1 mg) corresponding to scores greater than 9. Diazepam 10 mg TID and lactulose 20 ml TID was also given. The patient reported feeling better, but periods of confusion were noted. The patient was noted to be alert with clear speech, and oriented to place and month, but not year.

On November 14 at 05:45, the patient was found in the hallway threatening to leave requiring security to be called to assist in managing his behaviour. CIWA scores in the early morning were in the high 20s and ranged from 20 to 29 throughout the day. Heart rate was 88-116. A positive Confusion Assessment Method (CAM) screen for delirium indicated behaviour changes, attention focusing difficulty, disorganized thinking, disorientation, memory impairment, perceptual disturbances, psychomotor agitation and altered sleep/wake cycle consistent with delirium. The psychiatry service was consulted and proposed a diagnosis of delirium due to benzodiazepine intoxication citing the amount of benzodiazepines administered (total of 18 mg Lorazepam and 50 mg diazepam since admission) and the overall lack of autonomic symptoms. The patient's tremor was attributed to previously documented cerebellar dysfunction noted in the patient's chart. Moreover, since the patient's last drink was noted to be more than 72 hours prior, it was reasoned that his risk of severe alcohol withdrawal was declining. At this time, the patient was noted to be drowsy, disoriented to place and time, but oriented to name. His speech was noted to be slightly slurred and he was noted to have little insight into his condition. The CIWA protocol and all previous benzodiazepine orders were discontinued and the following new orders were implemented at 12:20: Loxapine 5 mg PO daily at noon, 10 mg PO daily at 17:00, and 20 mg HS, and loxapine 5-10 mg PO or IM q1h PRN with lorazepam 1 mg PO. That day the loxapine administered was 2.5 mg at 1:00, 10 mg at 16:30, 20 mg at 21:00 and 15 mg at 22:00.

During the morning of November 15, the patient triggered his bed alarm and was noted to be uncooperative. Heart rate was 65-73, and CIWA scores ranged between 7-21. He had received two PRN doses of loxapine and lorazepam over the last 24 hours, but the 12:00 loxapine dose was held and only 5 mg given at 17:00 because of drowsiness.

On November 16, the psychiatry service noted improvement of the delirium, but also over-sedation, and reduced

the loxapine orders to 2.5 mg PO daily at 17:00 and 5 mg PO HS. HR was 73-107. On November 17, the patient remained disoriented to place.

On November 18, the patient was agitated and made multiple attempts to leave the ward resulting in security being called to escort the patient back to bed. Later that day he was noted to be calm, cooperative and fully oriented by the medical teaching team; but in the mid-afternoon, he became uncooperative and agitated, and Security was called again to apply restraints. Loxapine and lorazepam were administered at 15:25. Delirium screening that day at 10:45 and 21:00 showed improved delirium, but with ongoing difficulty focusing attention, disorganized thinking and memory impairment. On November 19, the patient was still confused. On November 20, the patient was cooperative and discharged, and was instructed to follow up with his family doctor within one to two weeks for assessment of his confusion.

In summary, the patient's delirium began 48 hours after admission to hospital for alcohol intoxication, approximately 24 hours after implementation of standard benzodiazepine treatment for alcohol withdrawal. Delirium due to benzodiazepine toxicity was diagnosed despite ongoing tachycardia and other alcohol withdrawal signs. Treatment for the patient's delirium primarily using antipsychotics was implemented, and in the next four days was associated with intermittent oversedation, alternating with agitation requiring physical restraints, and during which time there was intermittent tachycardia and different interpretations of physical signs by different clinicians. By the 10th day in hospital, the patient's delirium and alcohol withdrawal signs had resolved including his pneumonia. In review, the patient's course in hospital more likely suggests a diagnosis of DT, which may have been exacerbated or prolonged due to under-treatment with benzodiazepines that was associated with administration of antipsychotics, as well as underlying pneumonia, which will be discussed in the following section.

DISCUSSION

We have described a case of delirium in a patient presenting to the emergency department after a fall secondary to alcohol intoxication, who had a recent history of daily alcohol use, and developed signs and symptoms of alcohol withdrawal, but in whom the diagnosis of delirium tremens (DT) was uncertain in the context of pneumonia

and potential benzodiazepine toxicity.

It is important for clinicians to be able to identify patients at risk of developing DT. Risk factors include: two or more days since last drink⁷, current or past seizure history^{8,10}, prior history of delirium tremens^{8,9,11,12}, concurrent acute infection⁸ or other acute or chronic medical illness^{7,12}, tachycardia at diagnosis of alcohol withdrawal^{11,13}, systolic blood pressure >145-150 mmHg at diagnosis of alcohol withdrawal^{10,12}, axillary temperature >38 degrees Celsius at diagnosis of alcohol withdrawal¹⁰, and alcohol withdrawal signs accompanied by an alcohol concentration >1 gram/L of body fluid⁸. The patient in this case presented with multiple risk factors for DT: his last drink was three days prior to developing delirium, he was treated for pneumonia while in hospital and had multiple comorbidities (e.g. diabetes, hypertension and cirrhosis), and demonstrated tachycardia and hypertension in the setting of an elevated blood alcohol level.

In retrospect, the clinical presentation of the patient, including the timing and evolution of his delirium suggests DT due to severe alcohol withdrawal – exacerbated by under-treatment, his acute medical illness and potentially the administration of antipsychotics since it is possible that antipsychotics caused drowsiness and lowered the CIWA scores thereby resulting in under-treatment of alcohol withdrawal. The treatment of DT is discussed below. Antipsychotic medications have generally been recommended against in patients withdrawing from alcohol, especially as mono-therapy, as they have been shown to lower the seizure threshold^{14,15}.

Delirium is common in patients with pneumonia. One study found that 45% of patients age 65 or older with community acquired pneumonia presented with delirium upon admission to hospital¹⁶. It is likely, given the diagnostic uncertainty, that the patient's delirium was multifactorial and complicated by his concurrent pneumonia.

The patient's delirium was first attributed to benzodiazepine toxicity. Importantly, up to 39% of delirium in the elderly has been estimated to be due to medications; benzodiazepines are among the most common medications that may lead to delirium¹⁷. Patients with benzodiazepine toxicity classically present with signs and symptoms of CNS depression and normal vital signs. They may present with slurred speech, ataxia, and depressed mental state.

The patient in this case was noted to be confused on

November 13 and a positive CAM screen confirmed delirium on November 14. In addition to delirium, signs and symptoms suggestive of DT included tachycardia, hypertension and agitation. His respiratory rate was elevated. Apart from the patient's delirium and slightly slurred speech, the clinical presentation does not fit well with a diagnosis of delirium due to benzodiazepine toxicity due to a lack of signs and symptoms of CNS depression (e.g. slowed breathing) and the patient's abnormal vital signs.

The conventional approach to treatment of alcohol withdrawal is benzodiazepines⁸. In the setting of DT, benzodiazepines can be administered intravenously. A variety of benzodiazepines and dosing regimens have been recommended, but in general, an individualized treatment approach focused on patient factors and symptoms is recommended^{8,19}. The CIWA protocol is commonly used to frequently assess patients' symptoms and adjust dosage accordingly.

Some patients may experience refractory DT despite very high doses of benzodiazepines. In such cases, some barbiturates (phenobarbital) and anaesthetics (propofol) have shown to be effective if administered in addition to benzodiazepines^{8,19}. Other medications have been used with and without benzodiazepines to treat alcohol withdrawal and DT, but the evidence for these is less compelling. Frequent and close monitoring of symptoms and vital signs is critical in patients with DT – especially in cases where treatment involves very high doses of medications and/or is complicated by active comorbidities.

Had the patient been correctly diagnosed with delirium tremens on November 14, the patient's delirium would have been treated with benzodiazepines as outlined

above rather than antipsychotics. This would likely have improved the patient's signs and symptoms and resulted in a shorter hospital stay.

This case highlights the importance of recognizing signs and symptoms of alcohol withdrawal and knowing how to distinguish and manage different causes of delirium when there is uncertainty about the etiology. Common causes of delirium in patients presenting to acute medical wards include medical illnesses (e.g. infection), medications (e.g. benzodiazepines), substance intoxication, and alcohol withdrawal (e.g. DT). DT, as described above, is a serious medical condition associated with significant costs to the patient and the healthcare system.

Key components of an assessment of potential DT, which can help rule in or out a diagnosis of DT, include a history focused on current and past alcohol consumption (e.g. timing, amount, type, previous seizure or DT), risk factors for DT, and clinical symptoms and signs of DT including confusion starting approximately 48-96 hours after cessation or reduction of alcohol intake, agitation, disorientation, hallucinations and signs of autonomic hyperactivity (e.g. tachycardia, hypertension, hyperthermia, tremulousness and diaphoresis).

As seen in this case, differentiating causes of delirium can be challenging and result in misdiagnosis of the etiology of delirium and subsequent under-treatment and/or inappropriate treatment. In the setting of suspected DT, when contraindications do not exist, the conventional treatment would be IV benzodiazepines and close monitoring of symptoms and vital signs to ensure optimal patient outcomes.

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TABLE 1: COMMON SIGNS AND SYMPTOMS OF ALCOHOL WITHDRAWAL(20)

Syndrome	Clinical signs and symptoms
Minor withdrawal (6 - 36 hours)*	Tachycardia Hypertension Tremor Diaphoresis Anxiety (mild) Headache Anorexia / GI upset Insomnia Normal mental status
Seizures (6 - 48 hours)*	Single or brief flurry of generalized, tonic-clonic seizures, short post-ictal period Status epilepticus (rare)
Alcoholic hallucinosis (12 - 48 hours)*	Visual, auditory +/- tactile hallucinations Normal orientation Normal vital signs
Delirium tremens (48 - 96 hours)*	Tachycardia Hypertension Delirium Agitation Fever Diaphoresis

*Onset after last drink

TABLE 2: VITAL SIGNS ON THE WARD BETWEEN NOVEMBER 11-20, 2013

	Nov. 11	Nov. 12	Nov. 13	Nov. 14	Nov. 15	Nov. 16	Nov. 17	Nov. 18	Nov. 19	Nov. 20
Heart rate	60-110	100-111	102-118	88-116	65-73	73-107	84-90	86-96	81-93	84
Systolic blood pressure	110-143	136-164	107-160	131-151	128-132	123-154	130-138	102-136	129-145	133
Diastolic blood pressure	51-77	62-78	49-80	67-78	64-78	61-76	62-67	60-68	59-79	65
Respiratory rate	18-22	16-20	16-20	16-18	18	18	18	18-20	20	18
Temperature	36.4-36.7	36.9	36.8-37.5	36.5-37.1	36.4-37.2	36.4-36.8	36.7	36.1-36.8	36.4-36.6	36.6

Two decades of the Swiss program based on the prescription of Diacetylmorphine, from a public health intervention to a treatment option

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ABSTRACT

The medical prescription of diacetyl morphine (heroin) treatment is an addition to the therapeutic arsenal for patients gravely dependent or addicted to heroin use and for whom other forms of therapy have failed. In Switzerland, the Federal Office of Public Health (SFOPH) has established directives and recommendations concerning prescription and administration of diacetyl-morphine.

La prescription médicale d'un traitement par diacétylmorphine (héroïne) s'ajoute à l'arsenal thérapeutique disponible pour les patients gravement dépendants à l'héroïne et pour qui les autres approches thérapeutiques ont échoué. En Suisse, l'Office fédéral de la santé publique (OFSP) a formulé des directives et recommandations quant à la prescription et l'administration de la diacétylmorphine.

The diacetyl-morphine treatment aims to provide access to healthcare and retention of the patient in the healthcare system. The therapeutic objectives are to promote health, to improve social integration and progress in treatment for the targeted group of patients fulfilling the criteria of diacetyl-morphine prescription

The Swiss program for the medical prescription of Diacetylmorphine is two decades old, initially introduced as a harm reduction measure in 1994 following the Swiss drug policy change of 1991. This program is an integral part of the four pillars Swiss drug policy (prevention treatment, harm reduction and repression). Over the years, its initial objective as a harm reduction measure has been replaced by its role as a treatment tool for which the harm reduction measure had laid the basis. This approach has enriched the therapeutic arsenal in the field of addiction treatments catering for the needs of the refractory heroin addicts.

The mid- and long-term results of heroin, assisted treatment (HAT), speaks in favor of this treatment rationale with effects on morbidity, mortality and a reduction in criminal involvement. These indicators are all related

to a significant reduction of intravenous use of illegal substances along with social stabilization.

Yet, the treatment program still remains one of the most controversial practices in medicine despite its documented effectiveness.^{1,2,3}

The program was introduced following an epidemic of heroin, overdose, HIV infections and the flourishing of open-air consumption scenes around large cities. Currently there are 21 centers, of which one of them is in a prison which dispense this therapeutic approach. Our center in Geneva, the only one in the French speaking region of the country has been operational since 1996.

The admission criteria for the prescription of diacetyl-morphine are⁴ the following:

- At least be 18 years of age,
- Severely heroin dependant for at least 2 years,
- Have undergone at least two inconclusive treatment episodes, without interruption, with recognized treatment methods
- Have physical, psychological impairments along with social distress caused by drug consumption.

The Swiss federal office of public health (SFOPH) delivers the authorizations for the prescription and oversees the program in collaboration with other partners.

In the context of treatment by the prescription of diacetylmorphine, the SFOPH fulfills the following tasks :

- Delivers authorisations to institutions, doctors and patients.
- Monitors the institutions and implements the relative controls in collaboration with the cantonal health authorities and Swissmedic.
- Coordinates the diacetylmorphine prescription network aiming to promote exchange, share expertise and transfer of knowledge
- Elaborates and supports publication of the manual on Treatment and prescription of diacetylmorphine.
- Coordination of the commission of diacetylmorphine prescription specialists
- Elaboration of an annual report on the diacetylmorphine prescription program

What conclusions can we draw from 2 decades of medical prescription of Diacetylmorphine?

For the last 10 years, the total number of patients is pretty much stable around 1500 whilst it was around 400 in 1994. The average age has been on the increase every year with a large age range (20-75 years). The number of estimated opiate users in Switzerland is 30'000 (for a total Swiss population of 7.8 million persons) and currently 55% of them are in treatment.

At least half the patients on average stay for 2,5 years in the program and the percentage of the long term, 15 years retention in the program, is around 1/5 of the patients in treatment.

As shown in Figure 1, the great majority (more than 85%) of opioid, based substitution, treatments are methadone based whilst less than 10% are Diacetylmorphine. The prescription of diacetylmorphine is not a first line treatment for opioid dependency. It is a relatively expensive and intensive treatment and is only provided in a strict framework, when all other commonly practiced therapeutic options are no longer effective for the patient.

FIGURE 1: OPIATE ASSISTED TREATMENT IN SWITZERLAND: NUMBER OF PATIENTS BY TREATMENTS. SWISS FEDERAL OFFICE OF PUBLIC HEALTH

This treatment approach offers the possibility of continued access to medical care for the severely afflicted patients in order to maintain them in the treatment system and also offers the possibility of increasing stepwise the care in addiction treatment for this complex group.

The conceptual model of the Swiss drug policy of 4 pillars⁵ has the merit of uniting the various actors on a

common platform in a consensual and coherent drug policy approach. The Swiss confederation's leadership role and the Swiss direct democracy greatly facilitated the acceptance of this harm reduction measure in the four pillars policy approach which is now legally bounded in the Swiss constitution following two referendums.

The four pillars conceptual model has evolved towards a 3 dimensional approach called the "Cube" (Figure 2). This concept integrates in one of the dimension's the 4 pillars approach, in another dimension, the different psychoactive substances and in the 3rd dimension, the level of consumption and behavioral risks, ranging from none, insignificant, problematic and dependent use. This view has the merit of identifying the potential risky consumers and also dependent users. This approach allows tailoring of a public health approach to the consumption of substances.

FIGURE 2: THE FOUR PILLAR CONCEPTUAL MODEL, THE "CUBE"

In conclusion, the prescription of Diacetylmorphine can be considered as a feasible, safe and integrated treatment approach enhancing access to healthcare for this complex group of patients.

Due to the lack of comparable policy analyses from other countries having medically prescribed Diacetylmorphine programs, the Swiss treatment program can merely be used as an example and a possible starting point for furthering comparative research⁶.

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ISAM 2014 Abstracts

The following is a selection of relevant abstracts from the 2014 ISAM Annual meeting in Yokohama, Japan.

ADDICTION AS A REWARD, STRESS AND EXECUTIVE FUNCTION DISORDER

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Drug addiction has been conceptualized as a chronically relapsing disorder of compulsive drug seeking and taking that progresses through three stages: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation. Via these stages, drug addiction impacts multiple motivational mechanisms and can be conceptualized as a disorder that includes elements of positive reinforcement and negative reinforcement. Three key neurobiological circuits are engaged in the motivational changes driving addiction that involve dysregulation in incentive salience- reward systems, sensitization of brain stress systems, and deficits in executive function systems. Specific neurocircuitry/neurochemical elements in these structures include the basal ganglia (incentive salience-reward deficits involving dopamine), the extended amygdala (recruitment of the brain stress systems involving corticotropin releasing factor) and the orbitofrontal/prefrontal cortex (executive function deficits involving glutamate). The combination of dysregulated incentive salience-reward function, sensitized stress systems and disrupted orbitofrontal/prefrontal executive function provides a powerful motivation for compulsive drug use and the loss of control over drug taking. Understanding

the neurocircuitry neuroadaptations in the reward, stress and executive function systems will provide new insights into identifying vulnerability to addiction and novel treatments for addiction.

GLOBAL PUBLIC HEALTH AND ADDICTION MEDICINE: FROM INTERNATIONAL POLICY FRAMEWORKS TO ICD-10 REVISION

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Use of alcohol, tobacco, drugs and other substances has a significant impact on global health: by any measure the global burden of disease attributable to substance use is bigger than the burden attributable to any other risk factor. Alcohol and tobacco use, highly prevalent in the world population, are among the most important contributors to poor health globally. In 2012 estimated 3.3 million deaths, or 5.9% of all deaths worldwide, were attributable to alcohol consumption. The Global strategy to reduce the harmful use endorsed by the governments of all WHO Member States provides international policy framework for action at all levels. Reducing the harmful use of alcohol is one of the 9 targets for the Global action on prevention and control of noncommunicable diseases (NCDs).

Addiction medicine professionals have important role in reducing public health problems due to substance use and addictions which goes beyond clinical practice in specialized services. Currently WHO is revising International Classification of Diseases (ICD), and ICD-11 is expected to be released in 2017. Clinical and health care utility is in the forefront of ICD revision. The current draft of ICD-11 maintains the diagnostic categories of “dependence” and “harmful use” with expanded boundaries of the concept of “harmful use”. Field testing of ICD-11 requires active participation of professional associations and practitioners from different parts of the world.

STRESS AND ADDICTIONS: NEUROBIOLOGIC INTERFACE

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The relationship between stress and addictions is complex. Early life adversity is a well-known risk factor for the development of addiction and stress is associated with relapse vulnerability. Preclinical research demonstrates that stress exposure enhances drug self-administration and reinstates drug seeking in drug-experienced animals. There are common neurobiologic systems involved in the stress response and in addictions including corticotropin releasing factor, the hypothalamic-pituitary adrenal axis (CRF/HPA), extrahypothalamic CRF and noradrenergic systems. In this presentation, neurobiologic relationships at the interface of stress and addictions and treatment implications will be explored.

MECHANISMS AND TREATMENT OF BEHAVIORAL ADDICTIONS WITH SPECIAL EMPHASIS ON INTERNET AND FOOD ADDICTIONS

Marc N. Potenza
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Background: The extent to which excessive engagement in non-substance-related behaviors may constitute addictions has been debated. The recent classification of gambling disorder together with substance-use disorders in DSM-5 was based on similarities between the disorders and lends additional credence to the concept of non-substance or behavioral addictions.

Methods: Data will be presented from studies into the biological underpinnings of substance-use and non-substance-use disorders involving excessive patterns of gambling, eating, Internet use, sex and other behaviors. Data from randomized clinical trials will be presented.

Results: Gambling disorder is arguably the best studied of the behavioral addictions to date. Data indicate multiple similarities, as well as differences, between gambling disorder and substance-use disorders. Considerable debate exists as to whether obesity or other eating-related disorders might be best considered within an addiction framework, with data suggesting particular similarities between gambling, substance-use and binge-eating disorders. Although less data exist for excessive engagement in other behaviors (Internet use, sex), emerging data suggest similarities with substance-use disorders. Given biological similarities, a question arises as to whether behavioral and pharmacological treatments efficacious in the treatment of substance addictions might prove helpful in the treatment of behavioral addictions, with data providing support for cognitive-behavioral therapies and opioidergic and glutamatergic agents.

Conclusions: An improved understanding of the biological factors underlying behavioral addictions is developing, and this understanding should lead to the greater availability of validated therapies.

PERSONALIZED TREATMENT IN ALCOHOLISM: PROMISE AND FIRST RESULTS

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Effect sizes from alcohol treatment trials are modest. The heterogeneity of patients may be one reason. In our Predict study (Mann et al 2009; 2013) we used biological measures such as genotyping and brain imaging (fMRI, receptor PET) to phenotype patients. We hypothesized, that patients, for whom alcohol acts as positive reinforcer could be separated from those for whom it is a negative reinforcer. The former were expected to be naltrexone responders, the latter to respond better to acamprosate. Results in 426 patients will be presented. Genetics, fMRI and some psychometric tests are supportive of our basic predictions.

Another approach to broaden treatment options concerns the choice of treatment goals. The European Medicines Agency (EMA 2010) has opened the door for testing a reduction of alcohol consumption. Three trials with the opioid modulator nalmefene were performed (i.e. Mann et al 2013). They offer an additional option for patients, who do perceive the need to cut down on their drinking, but are not ready to abstain from alcohol.

IMPLEMENTING THE INTERNATIONAL DRUG CONVENTIONS

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The International Drug Conventions were designed to care for the health and welfare of mankind. However, poor implementation of the conventions in its entirety and unbalanced allocation of resources have led to an approach which has undermined the demand reduction arm. Relevant areas will be discussed to encourage better implementation to protect civil society and those afflicted by diversion of controlled substances for uses other than scientific and medical purposes.

Ensuring availability and rational use of narcotic drugs and psychotropic substances for medical use is at the core of the United Nations drug control treaties.

However, access to these drugs is uneven.

These drugs remain inaccessible to the large majority of people around the world. On the other hand, overprescribing of opioid analgesics may lead to the diversion and abuse.

Article 38 of the Single Convention, in its amended version, reflected the need to adopt a multidisciplinary approach to the problem of narcotic drugs. There is a legal obligation to take all practicable measures for the prevention, early identification, treatment, education, after-care, rehabilitation and social integration of persons involved. This complex problem will need personnel training promotion and of awareness campaigns.

The International Narcotics Control Board is committed to ensuring a balanced implementation and thorough understanding of the conventions.

EMERGING EPIDEMIC OF HEPATITIS C INFECTION IN YOUNG INJECTORS

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Substance abuse and co-occurring infections of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) and associated morbidity and mortality are among the most significant health problems that world faces today. An estimated 153-300 million people abuse illegal drugs regularly worldwide and globally around 16 million people inject drugs. In addition, an estimated 170-200 million people are living with viral hepatitis C infection. Injection drug use is a major vector in acquisition and transmission of HCV infection. Up to 60% IDUs may be infected with HCV infection, while up to 90% of IDUs infected with HIV are also co-infected with HCV infection. Among IDUs worldwide, the incidence and prevalence of HCV infection is 50-90% and 10-30%/year, respectively. HCV infection is a serious blood-borne infection that causes liver cirrhosis, liver cancer and death. If untreated, up to 10% of HCV infected people may die from liver cancer each year. In 2007, more people died from HCV-associated complications than from those of HIV/AIDS. In an emerging epidemic, recent reports in the US have reported increases in HCV infection among young, 18-25 year old, non-urban IDUs in most US states. Increases in incident HCV infections

among young injectors who've recently transitioned from oral opioid abuse present an important public health challenge requiring a comprehensive, community-based response. This plenary lecture will discuss various aspects of substance abuse, HCV infection in young adults that have transitioned from oral prescription drug use to injecting drugs and leading to acquisition and transmission of HCV infection causing morbidity and mortality. It will also present the most current medical interventions for HCV infection and new research being funded by NIDA/NIH.

PRESCRIPTION DRUG ABUSE AND DIVERSION, A GLOBAL PROBLEM, STRATEGIES TO CURB THE ABUSE: BENDING THE CURVE OF OPIOID ANALGESIC ABUSE IN THE UNITED STATES

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Background: Abuse of prescription drugs is the leading cause of accidental death in the United States. In response, hundreds of federal, state and local interventions have been implemented. We describe trends in the diversion and abuse of prescription opioids using data through 2013.

Methods: We used 5 different programs from the Researched Abuse, Diversion and Addiction Related Surveillance (RADARS) System to describe trends in diversion and abuse of 6 opioid analgesics: oxycodone, hydrocodone, hydromorphone, fentanyl, morphine, and tramadol. The programs include law enforcement agencies, poison centers, substance abuse treatment centers and college students.

Results: RADARS System programs reported large increases in opioid diversion and abuse rates from 2002 to 2010, but then rates flattened or decreased 2011

through 2013. Poison Center fatality rates also rose and fell with a similar pattern.

Conclusions: Considered with other data sources, it seems possible that the long period of increasing prescription opioid abuse may be abating. The reasons for this observation are unclear but generate several alternatives that could affect the public policy debate regarding prescription opioid analgesics.

THE PROBLEMS OF PRESCRIPTION DRUG ABUSE IN KOREA AND TAKING ACTIONS TO OVERCOME

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Objectives: According to the criminal data related to illegal drug abuse in Korea, the most popular drugs were psychotropics. However, the majority of the illegal drug was psychostimulant including methamphetamine, MDMA not the prescription medication. Nevertheless, we cannot overlook the problem of prescription drug abuse owing to the serious hidden problems.

Methods: The result of survey with the non-psychiatric doctors in Korea about the prescription patterns of benzodiazepine will be presented. Recently, the National Evidence-based Healthcare Collaboration Agency reported the potential risks of over-prescriptions of Benzodiazepine in Korea. Some news reported that the problem of Propofol abuse of several celebrities. Those data was summarized.

Results: The benzodiazepines were prescribed quite diverse area not only for anxiety relieve or sleep induction but also for just relax of nearly most of impaired physical conditions. The percentage of people who filled BZD prescription of at least once was 8.4-18.6% during one year in all population without restriction of age. Most frequent prescribing active ingredient was diazepam, and gastro-duodenal disease was the most frequent indication for BZD prescription. (29.8% among out-patient claims and 14.7% among in-patient claims). BZD prescription of at least once during five years occurred

for a total of 22,361,449 patients (≥ 18 years old) using 5% sampling data. The average national prescription prevalence per 100 people per one year was 23.7%, 7.9%, 4.7%, and 3.2 % for BZD annual prescription of ≥ 1 day, ≥ 30 days, ≥ 90 days, and ≥ 180 days, respectively using total number of population (≥ 18 years old) during study periods. The risk for fracture was higher in patients with BZD prescription than people without BZD prescription. Most of the doctor had a mind to reduce benzodiazepine prescription but only the 17.6% of non-psychiatric doctors tried to discontinue the benzodiazepine prescription.

Conclusion: The online DUR (Drug Utilization Review) system was disseminated from general hospital to small private clinics nationwide. Through DUR system the authority keeps their eyes on the prescription pattern. For each drug that might have abuse liability limitation of dosage and duration of prescription is strictly monitored. Other ongoing counteract processed will be discussed.

ELECTRONIC ALCOHOL SCREENING AND BRIEF INTERVENTION

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Introduction: This presentation will summarise the findings from several controlled trials of electronic screening and brief intervention (eSBI) for hazardous and harmful alcohol use.

Method: Several randomised controlled trials have been conducted among (1) university students in Australia and New Zealand, (2) Maori and non-Maori students, and (3) out-patients at a large ambulatory care (out-patient) centre in Australia.

Results: Single-centre trials have shown significant reductions in alcohol intake, alcohol-related problems and, among university students, in academic performance. The effect size has been less in multi-centre trials. Whereas Maori students showed significant reductions in alcohol intake, there were only minor effects in non-Maori students. No reduction in alcohol intake and problems was evident among patients attending the ambulatory care centre.

Conclusion: As eSBI is extended to multiple sites, it

seems that the efficacy reduces. Likewise, when it is offered opportunistically in clinical settings, it may not have the effect seen among student populations or that therapist-delivered brief interventions have. Caution must be exercised in assuming the benefits of eSBI will be repeated in broad dissemination initiatives.

NIDA-ISAM FELLOWSHIP: EXCESSIVE INTERNET USE AND ITS CORRELATION WITH NEGATIVE EXPERIENCES IN 25 EUROPEAN COUNTRIES

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Introduction: The current debate on internet addiction is driven by question of whether it constitutes a distinct mental disorder. Our analysis of excessive internet use in adolescents offers an evidence for the line of research that distinguishes between addiction to the internet in general and addiction to specific online applications (as online games, cybersex, etc.)

Method: We worked with the EU Kids Online II survey data representative for children aged 11 to 16 years in 25 European countries (N=18,709). EIU was measured using five-items scale with one item for each of following criteria: salience, withdrawal, tolerance, conflict, and relapse. A set of regression models was used to assess the probabilities of various negative consequences for each EIU score.

Results: Surprisingly consistent pattern was identified across Europe when controlling for country differences with the score of 2.5 on EIU doubling the probability of misbehaviours, health and mental health problems, and negative online experiences.

Conclusion: Our results suggest that general internet addiction as measured by EIU scale occurs in children that suffer from much broader spectrum of both, online and offline, problems. Therefore, it might be better described as a symptom of behavioural problems rather than a separate psychological condition.

THE IMPACT OF THE GREAT EAST JAPAN EARTHQUAKE ON ALCOHOL, NICOTINE AND HYPNOTIC ABUSE AND GAMBLING IN DISASTER-STRICKEN AREAS

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Introduction: A huge earthquake and resulting tsunami struck north-eastern Japan in 2011 and caused widespread damage. It is believed that mental health problems, including substance abuse, increased in the area after the disaster.

Subjects and Methods: The subjects were 3600 people living where the damage caused by the tsunami was most severe and 2000 people living outside the disaster-stricken areas. Interviewers asked about drinking and smoking and also conducted semi-structured interviews based on the questionnaires which allowed the determination of whether subjects met the DSM-IV criteria for alcohol dependence. The following self-reporting questionnaires were asked: AUDIT, FTND, BDEPQ and SOGS.

Results: The prevalence of tobacco and hypnotic use and the frequency of subjects with high FTND and BDEPQ scores were higher in the coastal female group than the remaining two groups. The frequency of heavy alcohol use was associated with unemployment due to the disaster. The percentage of subjects with high SOGS scores was highest in the coastal area male group than the remaining two groups.

Conclusion: These results suggest that, in the disaster-stricken area, alcohol related problems and pathological gambling are increased in men while hypnotic and nicotine dependence is increased in women.

MEDICATIONS FOR TREATMENT OF ALCOHOLISM THAT DERIVE FROM THE DARK SIDE OF ADDICTION

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Drug addiction is a disorder characterized by compulsive drug intake, loss of control over intake and emergence of a negative emotional state during withdrawal. Addiction involves elements of impulsivity and compulsivity which when combined form an addiction cycle that provides heuristic framework with which to identify the neurobiological and neuroadaptive mechanisms involved in addiction, and as a result treatments for addiction. Based on this framework 3 stages of the addiction cycle have been identified that are relevant to alcoholism. These three stages: Binge-intoxication, withdrawal-negative affect and preoccupation-anticipation (“craving”) are reflected in key neuroadaptations that drive and maintain addiction. The binge-intoxication stage includes enhanced habit (stimulus- response) activity in the dorsal striatum. The withdrawal-negative affect stage reflects reward deficits in the ventral striatum (nucleus accumbens) such as dopamine and opioid peptides, but also stress surfeit in the amygdala such as recruitment of the brain stress systems including corticotropin releasing factor, dynorphin and norepinephrine. The preoccupation-anticipation stage reflects impairments in self-regulation mediated by dysregulation of executive function in the frontal cortex. Each of these stages provides a heuristic framework for treatment and can be targeted by existing and novel pharmaceuticals. Both naltrexone and acamprosate are effective medications for the treatment of alcoholism and are approved by the Food and Drug Administration of the USA. Naltrexone acts on the binge-intoxication state to block endogenous opioids and acamprosate acts on the preoccupation-anticipation stage to block glutamatergic activation. Future medications that focus on the withdrawal-affect stage and preoccupation- anticipation stage to restore the stress surfeit dysregulation characterizing these stages of the addiction cycle may have high potential as novel approaches to medications development for alcoholism.

TRAINING IN ADDICTION MEDICINE AROUND THE WORLD AND ISAM'S NETWORK OF NATIONAL CONTACTS

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Background: Addiction Medicine is taught in many different ways around the world. In order to ensure competent and well trained doctors for substance use patients, the training has to be well organized and in accordance with knowledge-based principles.

Methods: The board of ISAM has an educational officer. ISAM has established a network of medical doctors as national contacts in many countries. The purpose is to have a global network of doctors working in Addiction Medicine, to enable exchange of experiences, systems and ideas. ISAM has also performed a review in 2013 to get updated information about the state of Addiction Medicine training in different countries and also future plans.

Results: A network of 30 national contacts from the five continents has been established, but we welcome as many as possible. The results of the review on national training in Addiction Medicine will be presented in this workshop for 26 different countries.

Conclusion: ISAM has established a network of national contacts which we hope to expand further. This network and the update on the situation and plans for Addiction Medicine Training in different countries can be a valuable contribution to improving patient care in Addiction Medicine around the world.

NORWAY: A NEW FULL SPECIALTY IN ADDICTION MEDICINE

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Directorate of Health, Norway*

Background: The Norwegian Directorate of Health has been commissioned to help the Ministry of Health to establish a full specialty in Addiction Medicine.

Methods: A work group for the new specialty has been appointed by the Directorate of Health with medical doctors representing different parts of the system, user representatives and other professions. The work

group cooperates closely with the Norwegian Medical Association which has appointed a specialty board.

Results: The requirement for the specialty is five years of internship in accredited institutions. Three and a half year should be in Addiction Medicine, including one year in detoxification ward, one year in a department for out-patient treatment and half a year in a hospital department for in-patient treatment. Half a year should be in psychiatry. The last year the candidate can choose between two of the three following: Another half year of psychiatry, half a year in a somatic ward or half a year as general practitioner.

Discussion: Addiction Medicine will be a full medical specialty in Norway, probably as the first country of the world. Hopefully the first candidates in Addiction Medicine will start their training in January 2015.

CANNABIS USE DISORDERS: LATEST DATA ON CANNABINOID FORMULATIONS, ROUTES OF ADMINISTRATION AND TREATMENT

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Cannabis is the most frequently used illicit drug worldwide, and treatment admissions for cannabis use disorders have risen considerably in recent years. In addition, with broader societal acceptance of recreational and 'medical' cannabis in many countries, there are rapid changes in the formulation and route of administration, which have important implications for abuse liability.

This presentation will first describe the range of ways cannabinoids are currently abused: smoking plant-based cannabis, vaporization, oral formulations, synthetic cannabinoids. Second, we will describe the latest research on potential treatments for cannabis use disorder. Although psychosocial strategies improve treatment outcome, relapse rates remain high so the development of an approved medication for the treatment of cannabis dependence is a priority. Double-blind, placebo-controlled studies testing potential pharmacotherapies will be presented. This will include strategies to directly reduce cannabis intoxication, cannabis withdrawal (i.e., irritability, anxiety, disrupted sleep) and relapse to cannabis. To date, the most promising medications

include a slow onset, long-duration oral CB₁ receptor agonist, nabilone, an anti-hypertensive, lofexidine in combination with the oral cannabinoid, dronabinol, an opioid antagonist, naltrexone, and the GABAergic agonist, gabapentin.

These recent findings suggest that more treatment options may soon be developed for those seeking treatment for cannabis-related problems.

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HIGHLIGHTS FROM THE CANADIAN LONGITUDINAL STUDIES ON PROBLEM GAMBLING

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Introduction: To report on highlights of a longitudinal study of gamblers, the Alberta Leisure, Lifestyle, Lifecycle Project (LLLPP) as well as comparisons with the Ontario Quinte Study.

Method: Five LLL cohorts of gamblers (ages 13-15, 18-20, 23-25, 43-45, and 63-65) have been recruited through Random Digit Dialing (RDD) since February 2006. The cohorts are stratified by large and small urban centers and over-sampled for at-risk gamblers. Four data collections have occurred with initial telephone and face-to-face interviews, followed by web-based surveys. The selection of survey instruments reflected a biopsychosocial model of gambling.

Results: Recruitment at Time 1: N=1808 - Feb - Oct '06; Time 2: N=1495 - Nov '07 - Jun '08; Time 3: N=1316 - Jul '09 - Mar '10; and Time 4: N=1343 - Feb- Oct '11. (Overall Retention Rate 75.1% - 20 deceased). In addition, N=679 blood and saliva samples were collected. For comparison, the Quinte study had N=4121 and a Retention Rate 90.4% over 5 time intervals.

Highlights include: 1. an analysis of patterns of continuity/discontinuity of problem gambling over 5 years; 2. identification of variables best predicting future problem

gambling, coordinated with the Quinte study.

Conclusion: Longitudinal studies provide unique insights into the trajectory of gambling behaviors.

HEALTH ASSOCIATIONS WITH PROBLEM-GAMBLING SEVERITY: INSIGHTS FROM A LONGITUDINAL REPRESENTATIVE US SAMPLE

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Introduction: In the general population, problem-gambling severity lies across a spectrum, ranging from non-gambling through recreational gambling to problematic gambling. Cross-sectional data indicate that subsyndromal levels of gambling (i.e., not meeting the threshold for pathological gambling or in DSM-5 gambling disorder) are associated to varying degrees with poor health, particularly psychopathology. However, few studies have investigated incident psychiatric or general medical conditions with respect to problem-gambling severity.

Methods: Secondary analysis of data from waves 1 and 2 of the National Epidemiological Survey of Alcohol and Related Conditions was conducted. The 2 waves (collected from 2001-2002 and 2004-2005, respectively) included at wave 1 measures of problem-gambling severity (operationalized using inclusionary criteria for pathological gambling with individuals acknowledging one or more criteria categorized as having at-risk/problematic gambling - ARPG) and at waves 1 and 2 measures of psychiatric and medical conditions. Logistic regression analyses were conducted to examine the extent to which ARPG prospectively related to new (incident) psychiatric and general medical conditions.

Results: Relative to non-ARPG, ARPG was prospectively associated with: 1) incident nicotine dependence among adult women; 2) incident alcohol use disorders among adult men; 3) incident anxiety disorders and substance use disorders among older adults; and 4) incident cardiovascular conditions among older adults.

Conclusions: The findings of incident psychiatric disorders and cardiovascular conditions in relation to ARPG suggest that public health policies and initiatives should incorporate considerations relating to problem-gambling severity.

A PHARMACOGENETIC STUDY OF NALTREXONE IN KOREAN ALCOHOLICS

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Introduction: According to a recent pharmacogenetic study, patients with alcohol dependence (AD) who have one or two μ 8G alleles (G carriers) respond better to naltrexone than those who have the A/A genotype of the μ 8G mu opioid receptor (G non-carriers). This study was conducted to prospectively investigate the relationship between genotype and response to open label naltrexone treatment in Korean subjects with AD.

Methods: Sixty-three subjects with AD were prescribed naltrexone for 12 weeks in combination with cognitive behavioral therapy. Thirty-two subjects were adherent and took the medication on at least 80% of the treatment days (16 G carriers and 16 G non-carriers).

Results: The G carriers adherent to the naltrexone treatment took a significantly longer time than the G non-carriers ($p=0.014$). The G carriers treated with naltrexone had a 10.6 times greater relapse rate than G non-carriers ($p=0.072$).

Conclusions: These results demonstrate a higher therapeutic effect of naltrexone in Korean subjects with AD who have one or two μ 8G alleles compared to those who have the A/A genotype. Considering that Asians are more frequent G carriers for the μ 8G mu opioid receptor polymorphism than Caucasians, naltrexone might be more effective for treating AD in Asians than Caucasians.

ARE THERE ANY BENEFITS FROM REDUCING ALCOHOL CONSUMPTION?

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Alcohol contributes substantially to the global burden of disease and is the fifth leading disorder of DALYs in 2010 (GBD 2010 study) worldwide, and thus is one of the largest avoidable risk factors. Any reduction in dose of alcohol consumed, as well as in frequency of drinking occasions and the amount drunk on a single occasion will have an immediate impact in reducing alcohol-related injuries, the cardiovascular events and mortality related to heavy episodic drinking. Several examples demonstrate that total alcohol consumption has a significant impact on chronic consequences of excessive drinking. However, many treatment programs promote abstinence as the only/main acceptable treatment goal. Thus, many problem drinkers decline treatment programs aimed at abstinence. Offering both abstinence and no abstinence treatment goals to clients, permits a client-centered approach that contributes to alleviate client's resistance to change. The new DSM-5 introduces a diagnostic shift from the binary diagnostic criteria of alcohol dependence and alcohol abuse, to a single continuum of alcohol use disorders introducing a clear measure of severity such that treatment goals can be modified individually. In conclusion, reduction strategies offer an opportunity to address patient heterogeneity and lower the treatment threshold by bringing new patients into the treatment.

CAN ALCOHOL DEPENDENT PATIENTS REDUCE THEIR ALCOHOL CONSUMPTION?

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Abstinence has been the predominant treatment goal in alcoholism. There is no doubt that this approach has helped very many people around the world to overcome their alcohol problems. On the other hand, the abstinence goal is a very high threshold which may be one reason why we reach only about 10 % of patients in need for treatment.

A large US survey shows that 42 % of potential patients do not initiate treatment because they are not willing to quit alcohol completely. Against this background reduction of alcohol consumption is increasingly recognised as a valid and needed option.

The presentation will review diverse studies which deliberately went for a reduction (or control) of drinking as well as other studies which did not pursue this specific goal but which report various drinking outcomes including reduced drinking. The overview contains controlled psychotherapy trials as well as pharmacotherapy studies.

On the background of these data the European Medicines Agency (EMA) published guidelines in 2010 where the reduction of alcohol consumption is accepted as a valid goal in the treatment of alcohol dependent patients. So far several studies have been performed in this context, others are underway.

DSM 5 has collapsed the dependence and abuse categories. Therefore the reduction of alcohol consumption will have to be an integrated part of the management of patients with “alcohol use disorders”.

WHY ABSTINENCE IS IMPORTANT AS A TREATMENT GOAL OF ALCOHOL DEPENDENCE?

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Introduction: For a longtime, abstinence is the only way as a treatment goal of alcohol dependence. In recent years, however, harm reduction due to controlled drinking is supported as a additional therapeutic goal of alcohol dependence by some therapist.

In the side of abstinence, this article reviews the reasons of the abstinence to the treatment of alcohol dependence.

Method: Articles review which contents have abstinence or controlled drinking, moderation, harm reduction.

Results: Abstinence should be recommend as a final goal of Alcohol dependent patient for the following reasons

- 1) Loss of control is core concept of definition of addiction
- 2) Long term follow up studies on drinking of alcohol dependence have revealed the failure of controlled drinking finally
- 3) Abstinence is more safe and simple way than controlled drinking
- 4) Should abstain due to reinstatement, which is a phenomenon that even after a long term period of abstinence, a cup of alcohol could result in the past pattern of heavy drinking.
- 5) Should abstain for prevent brain damage caused by repeated alcohol withdrawal

Conclusion: Controlled drinking can be accepted as a way of treatment goal in mild alcohol use disorder cases but not in severe dependent person.

And useful method as a transient goal to lead abstinence who do not willing accept abstinence as a final goal.

The final goal of addiction treatment is not controlled drinking nor abstinence but recovery.

NICOTINE AND COGNITION IN SCHIZOPHRENIA

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Nicotine binds to presynaptic nicotinic acetylcholine receptors (nAChRs) in the brain and facilitates the release of acetylcholine, dopamine, serotonin, glutamate and other neurotransmitters known to be involved in cognitive processes. Nicotine systems in the brain play an important role in the neural basis of memory and attention. Smoking is highly prevalent in schizophrenia, and there is evidence for beneficial effects on neurocognition. Nicotine exposure to non-smoking schizophrenia patients and nicotine application after abstinence to smoking schizophrenia improved attention deficits. The study analyzing the interactional effects of diagnosis of schizophrenia and smoking history suggested a positive effect of smoking history on divided attention

in schizophrenia patients. Clinical studies using transdermal nicotine patches have demonstrated the efficacy of nicotine in improving cognitive performance, particularly sustained attention in nonsmokers with schizophrenia. Mecamylamine, a nAChR antagonist, worsened performance of attention compared to varenicline, a nAChR partial agonist, in schizophrenia. There was a treatment by diagnosis interaction, such that mecamylamine worsened performance of sustained attention compared to placebo and varenicline in schizophrenia patients, effects not observed in controls. These findings support a role for nAChRs in attention and suggest that those with schizophrenia may be particularly sensitive to nAChR blockade.

TAPERING OF METHADONE OR BUPRENORPHINE MEDICATION DOSE IN PREGNANCY. HOW MANY SUCCEED AND WHAT ARE THE NEONATAL OUTCOMES?

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Background: Opioid maintenance treatment (OMT) with methadone or buprenorphine is the treatment of choice for opioid dependent pregnant women. Many women want to lower their OMT-medication dose during pregnancy, thinking this will lead to less neonatal abstinence syndrome (NAS) for their neonates. Many professionals also try to influence women to lower their dose of methadone or buprenorphine during pregnancy.

Methods: A mixed prospective/retrospective cohort of 123 women were issued a questionnaire, also focusing on tapering of the OMT-medication dose during pregnancy. The medical information was confirmed by records from health professionals and from the hospitals.

Results: 63% of the women tried tapering their medication dose during pregnancy. The degree of tapering and the characteristics of the women who managed to taper their OMT-medication dose substantially during pregnancy will be presented, as well as the neonatal outcomes (growth parameters and NAS parameters) for the neonates of the women who tapered versus the neonates of the women who did not taper.

Conclusion: Some women manage to taper their

OMT-medication dose substantially during pregnancy, but the impact on the neonatal outcomes is limited.

SENSITIZED BRAIN REWARD SYSTEMS ACTIVATION IN OBESITY

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Introduction: Neuroscience evidence suggests that, similar to addiction, obesity involves neuroplasticity of brain reward systems. We aimed at examining whether individuals with different levels of adiposity had impaired activation of the brain reward circuitry.

Method: Forty-two adults with excess weight (21 with overweight and 21 with obesity) and 39 adults with healthy weight underwent functional resonance imaging (fMRI) scans during three tasks that involve the processing of varied rewards: foods (Willing to Pay), money (Monetary Incentive Delay) and social offers (Ultimatum Game). Tasks-related Blood-Oxygen-Level-Dependent (BOLD) signal was compared between the three groups using Statistical Parametrical Mapping software (SPM8) and correlated with adiposity levels using SPSS 20 software.

Result: Overweight but not obese individuals exhibit increased activation of core regions of the brain reward circuitry (orbitofrontal cortex, amygdala, and ventral tegmental area) in response to monetary rewards compared to healthy weight controls. Conversely, obese individuals relative to overweight individuals exhibit increased activation of the dorsal striatum in response to highly palatable foods, and of the anterior insula and anterior cingulate cortex in response to social rewards.

Conclusion: Overweight associates with enhanced sensitivity of motivational reward circuitry, whereas obesity involves hypersensitivity of the habit (dorsal striatum) and interoception (insula) systems.

THE ROLE OF NEAR-MISSES OUTCOMES AND INHIBITION LINKED TO PERSISTENCE IN A SIMULATED SLOT MACHINE TASK

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It is established that gambling “near-miss” outcomes (i.e. losing narrowly in a game of chance) promote persistent play. Although there have been recent advances in understanding the neurobiological responses to gambling near-misses, the psychological mechanisms involved in these events remain unclear. Recently, it has been shown (by using a laboratory slot machine task to deliver wins, near-misses and losses) that near-misses were more frequently perceived by problematic gamblers as an indicator of a future success (Clark et al., 2009). While impaired inhibition is implicated in case-control studies in pathological gambling, no studies have examined how inhibitory capacities moderate gambling behavior. In the current study, gamblers from the community played to a slot machine task which experimentally manipulate the delivering of win, miss, and near miss outcomes, and which comprises a non-mandatory extinction phase displaying only miss and near-miss outcomes. Participants were also tested with a stop-signal paradigm assessing prepotent response inhibition. The main findings of the studies are that (1) poor inhibition predicts persistence under extinction and (2) higher self-reported desire to play again both win and near-miss outcomes. This study for the first time highlighted the role of prepotent response inhibition in persistence (“chasing” behaviors) in simulated gambling.

INCREASED INTESTINAL PERMEABILITY IS RELATED TO GUT BACTERIAL DYSBIOSIS AND BEHAVIORAL MARKERS OF ADDICTION SEVERITY IN ALCOHOL-DEPENDENT SUBJECTS

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Alcohol dependence has traditionally considered as a brain disorder. Alteration of gut microbiota composition has been recently shown in psychiatric disorders, which suggest the possibility of gut to brain interactions in the development of alcohol dependence.

The aim of the present study was to explore whether the changes in gut permeability are linked to gut microbiota composition and activity in alcohol-dependent subjects. We also investigated whether gut dysfunctions are associated with the psychological symptoms of alcohol-dependence. Finally, we tested the reversibility of the biological and behavioural parameters after a short-term detoxification program.

We found that some, but not all, alcohol-dependent subjects develop gut leakiness which was associated with altered composition and activity of gut microbiota. Moreover, subjects with gut dysfunctions remained with higher scores of depression, anxiety and alcohol craving after three weeks of abstinence. These results suggest the existence of a gut-brain axis in alcohol-dependence which implicates the gut microbiota as an actor in the occurrence of the gut barrier and behavioral disorders. Thus, gut microbiota appears as a new target in the management of alcohol-dependence.

CHRONIC ETHANOL CONSUMPTION: ITS EFFECTS ON LIVER INFLAMMATION

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Alcohol-induced alterations in cell function, hepatic inflammation, and fibrosis are prominent features of liver disease in general and of alcoholic liver injury in particular. The link between these processes, however, remains unclear. A virtually universal characteristic of liver injury and subsequent inflammation is the induction of hepatocellular damage, and work from our laboratory has extensively studied the effect of ethanol administration on the hepatocyte and the process of endocytosis by these cells, using the asialoglycoprotein receptor (ASGP-R) pathway as a model. Our recent studies have shown that impaired uptake of several ligands by the ASGP-R (cellular fibronectin, carcinoembryonic antigen, and apoptotic bodies) leads to an ethanol-induced accumulation which then contributes to enhanced activation and cytokine production by non-parenchymal cells such as Kupffer cells and liver endothelial cells. The interaction of these ligands with the sinusoidal cells of the liver, as well as the cooperation and regulation between the different cell types after ethanol administration warrants further investigation and is the focus of talk. In our work we aim to acquire a better understanding of the cross-interactive associations that occur between the cell types following chronic ethanol administration, and which contribute to inflammation.

INFLUENCE OF SYSTEMIC INFLAMMATORY PROCESSES ON BRAIN IMMUNE SYSTEM

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Alcohol-induced inflammation plays an important part in the induction of alcohol induced brain damage. Increased peripheral inflammation, with the production of pro-inflammatory cytokines, possibly as a result of bacterial interaction with alcohol, acetaldehyde toxicity, macrophage stimulation or other factors, may act as important chemical messengers, which are able to traverse the blood brain barrier, BBB, and affect central

nervous system function. Indeed in adolescent binge drinkers, changes in the plasma ratios of pro-inflammatory to anti-inflammatory cytokines are evident. Once these cytokines have crossed the BBB, they may interact with receptors on glial cells thus enhancing the production of pro-inflammatory mediators which may lead to cognitive dysfunction. Since glial cells play an important role in the removal of neurotransmitter at the synaptic cleft, their activation may adversely affect this process thereby further contributing to cognitive dysfunction and depression. In addition increased glutamate excitotoxicity, as a result of alcohol detoxification, may contribute to the pro-inflammatory milieu. Animal studies have shown that the suppression of such an inflammatory response in the brain induced by chronic alcohol abuse and binge drinking by the administration of taurine analogues is beneficial in reducing both the inflammation and excessive glutamate production.

CANNABIDIOL: LONG-LASTING AMELIORATION OF VULNERABILITY STATES ASSOCIATED WITH RELAPSE RISK AS DETERMINED IN ANIMAL MODELS OF DRUG SEEKING, ANXIETY, AND IMPULSIVITY

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Drug addiction is a chronically relapsing disorder. Susceptibility to relapse can be traced to multiple factors: craving elicited by drug-related cues, anxiety, hypersensitivity to stress, and impaired impulse control. Relapse prevention treatments that concurrently target these vulnerability states may offer significant clinical advantages. Cannabidiol (CBD), the main non-psychoactive component of cannabis sativa, may provide such a profile of actions. CBD reduced ethanol and cocaine seeking in animal models of relapse during 7-days of treatment. Remarkably, drug seeking remained fully attenuated as late as 5 months after treatment termination. CBD also reduced anxiety-like behavior as measured in the elevated plus maze test, both during and after CBD treatment. Finally CBD reversed high impulsivity, measured by a delay discounting task, in

rats with an ethanol dependence history. CBD neither interfered with behaviors motivated by non-addictive natural reward, nor altered spontaneous activity. The findings reveal two unique clinically relevant dimensions that characterize the actions of CBD: (1) beneficial actions relevant for multiple vulnerability states associated with drug craving and relapse, and (2) long-lasting effects with only brief treatment. Thus, CBD may exert neuroregulatory actions that restore normal function to brain regulating reward, incentive motivation, impulsivity, stress and anxiety. (Support: NIH-NIAAA/NIDA AA01801, DA07348).

PREDICTORS OF INSOMNIA SEVERITY AMONG ALCOHOL DEPENDENT PATIENTS

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Introduction: Sleep problem is a frequent complaint of alcohol-dependent individuals during chronic use of alcohol, acute withdrawal, and even after sustained abstinence. Insomnia is associated with complaints of sleep-onset, sleep-maintenance, early morning awakening and nonrestorative sleep.

Methods: Totally 364 alcohol-dependent individuals were assessed at baseline and 6-month period intervals across a 2.5 year study period. Each assessment included the Time-Line Follow-Back interview (TLFB), the Sleep Problems Questionnaire (SPQ), and the Brief Symptom Inventory (BSI). All statistical analyses were performed using Hierarchical Linear Modeling.

Results: The prevalence of insomnia at baseline was 45.3% with an average SPQ score of 9.2 ± 5.6 . When modeled separately, both quantity of drinking ($p < .01$) and depression ($p < .001$) predicted insomnia severity, controlling for time, age, and gender. Drinking also predicted depressive symptoms ($p < .001$), and its effect on insomnia was mediated by depression severity ($p < .001$).

Conclusion: The main finding of this prospective study was that depressive symptoms mediated the relationship between drinking and insomnia severity, controlling for time, age and gender. The current study implies that attention to depressive symptoms in addition to alcohol consumption is an important component of reducing insomnia severity when treating alcohol-dependent patients.

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REINFORCEMENT EXPECTANCIES AS PREDICTORS OF DRINKING PROBLEMS AMONG SOLDIERS: USE OF THE ALCOHOL EFFECTS QUESTIONNAIRE (AEFQ) IN THE FRENCH ARMY

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Background: The aim of the study was to evaluate which alcohol use expectancies could predict harmful use in the French Army, to identify some hypotheses concerning socializing or coping effects.

Methods: A cross-sectional survey, using self-administered questionnaires, was conducted in two Army units in 2011 ($n=249$). Drinking disorders were identified using the Alcohol use disorders identification test (AUDIT). Alcohol expectancies were measured with the Alcohol Effects Questionnaire (AEFQ). A cluster analysis was performed to identify AEFQ dimensions in our sample. Relationships between AUDIT and AEFQ were explored using multinomial logistic regression.

Results: According to AUDIT, 28.8% of soldiers had a hazardous use without dependence and 19.9% were dependent. The AEFQ had a good internal coherence with a 0.78 global alpha coefficient. The scales identified by the cluster analysis in our sample fitted those retained in the originally validated AEFQ, with a correspondence

ranging from 60% to 100%. In multivariate analysis, the scale Social and physical pleasure was associated with increasing hazardous use and subjects who had greater Global positive and Social and physical pleasure scales were more at risk of dependence.

Conclusion: The present study, in line with previous research in terms of importance of alcohol use disorders among military personnel, suggests that soldiers may not only use alcohol as an individual strategy to cope with underlying depressive disorders, but also as a collective strategy to increase group bonding to cope with the difficulties of military profession.

PSYCHIATRIC COMORBIDITY AND EXCESS ALL-CAUSE AND CAUSE-SPECIFIC MORTALITY IN OPIOID ADDICTS

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Introduction: The challenge of personalised medicine is to identify components of addiction that are relevant to an individual in a way that treatment and drug overdose preventions can be tailored. Opioid misusers continue to have recognised extremely high mortality but the influence of psychiatric comorbidity in excess all-cause and cause-specific mortality is questionable.

Methods: Opioid-dependent (OD) patients were identified in London-based patient register, which contains records on over 220,000 cases linked to national mortality tracing. We used Cox regression to model the effect of psychiatric co-morbidity on mortality, controlling for a broad range of potential confounders.

Results: We identified 4837 OD patients with 176 deaths. The presence of comorbid personality disorder (PD) and alcohol use disorder (AUD) was found to be associated with increased all-cause mortality in all models, including the fully adjusted model. AUD was associated with two-fold increased risk of fatal overdose and seven-fold risk for liver-related deaths. Individuals with OUD and comorbid PD had almost four-times greater risk of liver related deaths compared to those without PD.

Conclusions: The study highlights the importance of assessment for PD and alcohol misuse among opioid addicts in order to identify individuals at substantially elevated mortality risk for a more personalised approach to their medical care.

This research is part of a larger project, which focusses on electronic-based personalised medicine in drug addiction. The complete research plan as well as research October '14 research update will also be provided.

NEUROLOGICAL SYMPTOMS, DEPENDENCE AND BEHAVIOR CHANGES ASSOCIATED WITH KHAT CHEWING IN JAZAN REGION, KINGDOM OF SAUDI ARABIA

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Background: Khat chewing is highly prevalent among males (up to 37.7%) at Jazan region in the far southwest of Saudi Arabia. Most of Khat quitters showed some withdrawal symptoms and better health after quitting. However, Khat chewers consider khat chewing as a social habit and deny khat dependence.

Objectives: To assess neurological symptoms associated with khat chewing, evaluate the behavior of khat chewers towards the chewing practice, measure psychological dependence among khat chewers.

Methods: A male volunteer study was conducted in Jazan region, Saudi Arabia. Seventy two khat chewers and seventy five non-chewers were recruited in the study. All participants filled a structured questionnaire asking about the neurologic symptom that was developed from the Lundberg Q16 questionnaire. Behaviors related to khat chewing were evaluated using modified questionnaire from Fagerstorm; 1978, Griffiths; 1998 and Kassim and Croucher; 2006 questionnaires. Khat dependence was measured using Severity of Dependence Scale (SDS) of khat lastly modified by Kassim et al; 2010.

Results: Khat chewers showed higher prevalence of neurological symptoms than non-chewers. The main neurological symptoms were loss of appetite, nausea and vomiting, feeling irritable, fast heart rate, and difficulty

with balance. 52% of khat chewers were dependant with median SDS score of 4.5. Most of chewers (70%) were behaviorally low on the behavior scale. Dependant chewers showed higher frequency of neurological symptoms, mainly; dizziness, nausea and vomiting, being abstained and inability to sleep by night.

Conclusion: Khat chewing is associated with disturbance in behavior. Around half of khat chewers are dependent on khat. Objective evaluation is required to measure khat dependency.

COGNITIVE IMPULSIVITY AND CHRONIC OPIOID USE

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Introduction: Previous studies have provided inconsistent evidence that chronic exposure to opioid drugs, including heroin and methadone, may be associated with impairments in executive neuropsychological functioning, specifically cognitive impulsivity.

Methods: Participants with validated histories of illicit heroin use (n=24), former heroin users stabilised on prescribed methadone maintenance treatment (MMT) (n=29), licit opioid prescriptions for chronic pain without history of abuse or dependence (n=28) and healthy controls (n=28) were recruited and tested on measures of cognitive impulsivity, motor impulsivity and non-planning impulsivity.

Results: Stable illicit heroin users showed increased motor impulsivity and impaired strategic planning. Additionally, they placed higher bets earlier and risked more. MMT participants deliberated longer and placed higher bets earlier but did not risk more. Chronic opiate exposed pain participants did not differ from healthy controls on any measures on any tasks.

Conclusion: These data support the hypothesis that different aspects of neuropsychological measures of impulsivity appear to be associated with exposure to different opioids and also to the syndrome of opioid dependence. This could reflect either a neurobehavioural consequence of opioid exposure, or may represent an underlying trait vulnerability to opioid dependence.

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