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Fine-Tuning Our Clinical Guidelines!

In compiling the components of this issue, I couldn’t help but reflect on the broad scope of our chosen field of practice. Certain areas have a plethora of clinical guidelines such as in the management of opiate dependence; others have close to none to steer us like in the recovery process. Not all sets of guidelines are of the same empirical quality. Journals are a good platform for clinicians and researchers alike to offer a constructive critique of the “rules” and help improve their next edition.

The last 30 years or so have been marked by the realization that the majority of our patients suffer from one or more comorbidity in addition to a substance use disorder. The lead article from Drs. Balderston and Crockford dissect the interaction between a psychotic disorder and cannabis use. Starting with a case vignette, the authors delve into the challenges of the differential diagnosis, the selection of medication and provide a stepwise guide to the integrated management of both disorders. This sophisticated clinical presentation is a welcomed model for other similar submissions to enhance our clinical skills.

The next two papers challenge a current Canadian screening guideline. The side-effect profiles of prolonged administration of several medications including methadone have received enhanced scrutiny of late and the preoccupation with QT prolongation and eventual “torsades de pointes” dates back to the early 2000’s. Dr. Worster, et al, leads with a thought provoking analysis of the variability of QT intervals in methadone maintained patients. The results from repeated ECG’s highlight difficulties in the accurate identification of QT prolongation because of intrinsic patient variability in QT length and limited accuracy of the automated measurements. Because of the clinical significance of this finding, a commentary from Drs. Nolan and Wood complements Dr. Worster et al’s paper. In summary, the utility of routine ECG screening in methadone maintained patients is challenged. These articles are good examples of the potential use of our Journal scrutinizing our guidelines.

Lastly, one of the benefits of the affiliation of CSAM-SMCA with ISAM is the ability to select from the many international submissions at the ISAM annual conference, a number of abstracts considered to be of relevance to our Canadian practices or at least potential early warnings of future developments. These abstracts once more further reflect the scope of our activities.

Clinical guidelines are benefitting from several international systematic efforts to collate the empirical evidence available. Updates in neurobiology and recent pharmacological clinical trials are presented, some arising out of necessity from the prohibition of the prescription of methadone in Russia. Also of note, is an update on the SALOME study in Canada. International contributions on alcohol, behavioral addictions and comorbidities are reported. Natural disasters are a common occurrence at the global level; a report on the epidemiology of drug use post-tsunami that struck northeast Japan in 2011 is presented. The concluding abstracts report on efforts to train our next generation in our field as well as the barriers to be overcome.

We are happy in this issue to extend a special welcome to two of our current trainees, Dr. Balderston and Dr. Nolan. The quality of their submission bodes well for the future of our field.

Hoping you enjoy this issue.

Nady el-Guebaly, MD
Editor-in-Chief, CJA-JCA
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Management of the Psychotic Substance Using Patient

Rhea Balderston, MD (Corresponding Author)
Psychiatry Resident, University of Calgary, Department of Psychiatry, Psychiatry Administration, 2nd Floor, Special Services Building, 1403-29 Street NW, Foothills Medical Centre, Calgary, AB T2N 2T9
Phone: 403-944-1271 • Fax: 403-270-3451
E: rhea.balderston@albertahealthservices.ca

David N. Crockford, MD, FRCP
Associate Professor, University of Calgary, Department of Psychiatry, C203, 1403-29 Street NW, Foothills Medical Centre, Calgary, AB T2N 2T9
Phone: 403-944-4791 • Fax: 403-944-2165
E: david.crockford@albertahealthservices.ca

Case: Chris is a 21-year-old male who lives at home with his parents and is in his 3rd year of Engineering. He is currently on academic probation for poor attendance and failure to complete assignments. He is brought to see you in your office by his parents, due to complaints from neighbours that Chris has been leaving threatening messages in their mailboxes. Chris complains that he can hear his neighbours talking about him and believes that they have planted a video-camera in his home, as they comment on his every action. He has been hearing their voices for the past 3 weeks, but has had trouble organizing his thoughts for at least 3 months, leading to his declining academic performance. Over the past year he has been spending progressively more time alone at home, playing video games and writing about life and its meaning. He quit playing pickup hockey, and hasn’t seen his friends for months. Chris started smoking cannabis at the age of 17, initially about once per month at parties, but in university his use increased to weekly. Six months ago he lost a part-time job in landscaping, and his use increased again to 1 gram daily. His last use was 2 weeks ago, when he stopped because he wondered if it was making him paranoid. Despite this, his beliefs about his neighbours have only intensified. He has no prior psychiatric history or family history of psychiatric illness. On mental status exam he is guarded with poor hygiene and blunted affect. He appears to be responding to voices and his thought form is tangential.

Chris’ presentation is consistent with both a cannabis use disorder and a psychotic disorder. Approximately one-third of first-episode psychosis patients have a cannabis use disorder3, and the lifetime prevalence of a substance use disorder (SUD) in patients with schizophrenia is as high as 57%4. Cannabis intoxication can cause transient psychotic symptoms in healthy subjects, however, in healthy individuals these symptoms typically resolve in a matter of minutes or hours4-5. While the majority of people that use cannabis do not go on to develop a chronic psychotic disorder4, regular cannabis use appears to increase the risk of developing schizophrenia in individuals who are somehow biologically predisposed4-15, though as of yet there are no definitive markers beyond a family history of psychosis/schizophrenia. Finally, substance use has been associated with earlier onset of schizophrenia1-2 and the risk of schizophrenia is six times higher in heavy users of cannabis as compared to non-users8.

DIFFERENTIATING SUBSTANCE-INDUCED PSYCHOSIS FROM AN INDEPENDENT PSYCHOTIC DISORDER

As is often the case in clinical practice, particularly in young adults with a first episode of psychosis, it is initially unclear whether Chris’ symptoms are cannabis-induced or part of an independent psychotic illness. Delineating the correct diagnosis is critical for treatment planning to avoid future non-adherence, treatment failure and recurrent hospitalizations17-21. While many persons with a cannabis use disorder presenting with psychotic symptoms have these remit within a few days to a week of abstinence, some will go on to have persistent psychosis even with abstinence from cannabis. According to DSM-V, there are three situations that would suggest a diagnosis of a primary psychotic disorder rather than one which is substance-induced: 1) symptoms precede the onset of substance use, 2) symptoms persist for a substantial period of time (one month) after discontinuation of substance use, or 3) there is evidence of previous psychotic episodes that were not substance-related22. The described case highlights the role of patient age, timing of symptoms in relation to cannabis use, amount of cannabis used, type and severity of symptoms, family history, and treatment response in determining the best diagnosis. Chris is 21 years of age. While this falls within the highest risk age category for men to develop schizophrenia, it also falls within the peak age for substance use. Over half of
male schizophrenia patients have their first admission to psychiatry before the age of 25\textsuperscript{16}. However, the peak age for substance use is between 15 and 25 years, so in the case of Chris, his age does not help to sort out the diagnosis. A later onset of psychosis, past the period of greatest vulnerability, would be more suggestive of psychosis secondary to a substance or general medical condition.

Although retrospective patient report of \textit{timing of substance use versus symptom onset} is prone to recollection bias, it can give useful cues. Chris’ cannabis use predates his symptoms of psychosis, and the development of his psychotic symptoms coincides with increased use to initially suggest a cannabis-induced psychosis. However, he reports ongoing and intensifying symptoms despite abstinence for 2 weeks, which would be more consistent with a primary psychotic disorder. Further, it is not clear whether his decline in function represents prodromal symptoms of psychosis preceding the overt presence of delusions and hallucinations, or the impact of cannabis use impairing cognition and motivation. Collateral history from family may help to further identify timing and intensity of psychotic symptoms, as patients with psychosis often under-report their symptoms. Sometimes patients may even identify their cannabis use as the culprit to avoid a diagnosis of a primary psychotic disorder, which comes with needing to be on an antipsychotic medication for 1-2 years after a first episode\textsuperscript{19}.

Determining the \textit{quantity and frequency of cannabis use} is helpful, but also difficult. The potency of cannabis varies greatly. Higher potency cannabis often sells at a higher price\textsuperscript{24}, thus it may be helpful to ask patients how much money they spend on cannabis per week, if they can poorly quantify otherwise. Studies of confiscated cannabis over the past two decades indicate that the concentration of delta-9-tetrahydrocannabinol (THC) has increased by over 200%, while the concentration of cannabidiol (CBD) has decreased\textsuperscript{25-26}. Higher ratios of THC to CBD have been associated with higher rates of cannabis-induced psychosis and schizophrenia-like symptoms\textsuperscript{27}. Urine cannabis levels corrected for urine creatinine may provide a clue: levels markedly above cut-off values suggest a cannabis-induced psychosis, while levels minimally above cut-off values or below suggest a primary psychotic disorder. Daily use would be more suggestive of a cannabis-induced psychosis, whereas occasional use would be more indicative of a primary psychotic disorder.

The \textit{type and severity of psychotic symptoms} Chris is experiencing include fairly typical paranoid delusions, classic auditory hallucinations, thought form disorder, and potential negative symptoms including avolition and neglect associated with a decline in function. His symptoms meet full criteria for a psychotic disorder, which is more suggestive of a primary psychotic illness than if he only met some of the criteria. Less than full diagnostic criteria, visual hallucinations, absence of negative symptoms, clouding of consciousness consistent with intoxication, and lack of a thought form disorder would be more suggestive of a cannabis induced psychosis. The fact that Chris’ behaviour is directly influenced by his delusions further emphasizes the severity of his psychosis and its likely primary nature. Given that he is actively psychotic, a thorough review of safety issues should be completed to rule out aggressive or homicidal ideation, intent or plans to harm others (especially the neighbours in this case) and any thoughts or plans for suicide. Safety concerns should prompt serious consideration of hospitalization and certification.

The decline in functioning, both socially and academically, could represent a psychotic prodrome or negative symptoms, but it could also relate to cannabis use. Often the answer only comes with regular re-assessment over months of abstinence. If it is cannabis-related it often remits, as opposed to negative symptoms that persist and sometimes worsen.

Finally, a lack of \textit{family history} of psychosis is fairly common even in persons with primary psychotic disorders. However, first episode psychosis patients with a first-degree relative that has been hospitalized for any psychiatric reason are 1.9 times more likely to eventually receive a diagnosis of schizophrenia, as opposed to first episode patients with no family psychiatric history\textsuperscript{28}. A family history of substance use disorders can guide diagnosis towards a substance-induced cause, whereas a family history of psychosis would make the diagnosis of a primary psychotic disorder more likely.

Given the persistence of Chris’ symptoms despite abstinence, classic auditory hallucinations, and presence of a thought form disorder in the context of a clear sensorium, his presentation is highly suggestive of a primary psychotic disorder that has been unmasked or exacerbated by his cannabis use. At this point it is reasonable to initiate treatment with an antipsychotic medication rather than waiting for further abstinence. This is especially true if there are safety concerns, drug screen results are consistent with abstinence, and/or if collateral history suggests a greater severity of psychotic symptoms.

**THE ROLE OF ANTI-PSYCHOTIC MEDICATIONS**

Ideally, management of persons with co-morbid psychosis and SUD should occur in an integrated fashion,
in order to maximize effectiveness and minimize dropout. If it seems likely that there is a primary psychotic illness, antipsychotic medication should be initiated and maintained for at least 1-2 years. For persons with co-morbid psychosis and SUD, the same pharmacologic treatment guidelines should be followed as would be the case if they did not have a SUD. To date, there is little to no evidence for using any one antipsychotic over another. Antipsychotic choice should be guided by prior individual or family treatment response (if any), patient preference, side effect profile, and likelihood for greatest adherence. Of note, however, is that persons with co-morbid psychosis and SUD tend to be more prone to extrapyramidal symptoms (EPS), which are particularly associated with conventional antipsychotics (CAP). Additionally, CAPs do not reduce substance use in psychosis patients due to their potent D2 receptor blockade, which may prevent the recovery of normal function in the brain’s reward circuitry. For these reasons, treatment with atypical antipsychotics (AAP) is generally preferred.

Among the AAPs, Clozapine has the most evidence for reducing cravings and substance use in dually diagnosed patients. In addition, it may have the benefit of having fewer cognitive side effects, allowing patients to use coping skills for substance use reduction learned in treatment. However, Clozapine use is restricted to only those persons who have failed 2 adequate trials of other antipsychotics and are deemed treatment-resistant, due to its risk of agranulocytosis, other blood dyscrasias, seizures, and orthostatic hypotension, requiring weekly blood monitoring and close follow-up. The relative benefit of Clozapine over other AAPs suggested in the literature may also reflect selection bias rather than a real finding. Studies to date have been retrospective in nature, involving patients selected to go on Clozapine who have been adherent to treatment and follow-up. Furthermore, most persons only stay on Clozapine if they have a positive treatment response. Thus, the benefits seen on SUD behaviour may reflect qualities of the selected group that lead to positive psychosis treatment outcomes, rather than specific effects of Clozapine. Prospective studies are required.

Of the remaining AAPs, there is slightly more evidence for Olanzapine, though there is emerging evidence for Risperidone, Quetiapine, and Aripiprazole. In Chris’ case, one may consider using Olanzapine or Quetiapine first, given their decreased likelihood of causing EPS compared to Risperidone, and lower potential for akathisia/restlessness compared to Aripiprazole. In addition, the sedation and appetite support provided by Olanzapine and Quetiapine may be of benefit, given that sleeplessness and lack of appetite are common when people discontinue regular cannabis use.

As is the case with non-SUD patients, oral antipsychotics should be offered first, with injectable antipsychotics reserved for patients in whom adherence is an issue. Non-adherence with antipsychotic treatment, however, is more the norm than the exception. In the CATIE (Clinical Antipsychotic Trials for Intervention Effectiveness) Schizophrenia Trial, the oral AAPs Olanzapine, Risperidone, Quetiapine, Ziprasidone and the CAP Perphenazine were compared for efficacy. All of the antipsychotics were essentially equal in effectiveness (both AAP and CAP), albeit with slightly different side effect profiles. Olanzapine, despite causing significant weight gain, was found to be the agent adhered to longest, but the most striking feature of CATIE was that for all antipsychotic groups, fewer than half of the patients assigned were still taking their treatment at one year despite rigorous and supportive follow-up care. For medication non-adherence, a trial of an injectable antipsychotic may be warranted, but EPS may be more common.

The duration of antipsychotic treatment for patients with co-morbid psychosis and SUD is the same as for patients without SUD: minimum 1-2 years for a first episode, and at least 5 years, if not indefinitely, for 2 or more episodes. If there are ongoing psychotic symptoms, antipsychotic treatment should be continued, even though a person may have had only one episode and have been treated for 1-2 years. Particular attention to adherence and follow-up are especially important in this population due to the increased risk of medical and social comorbidities.

INTEGRATING PSYCHOSIS AND ADDICTION TREATMENT

In general, when patients present with an addiction and a psychiatric disorder, best outcomes occur when both disorders are treated in an integrated fashion. Curiously, a recent review by Wisdom and colleagues found that persons with early psychosis significantly reduced their substance use (primarily alcohol and cannabis) with treatment of their psychosis alone. The addition of specialized addiction treatment did not
establish a significant difference in rates of substance reduction or abstinence. The psychosis treatment only programs did provide psycho-education and monitoring of substance use, known to be of benefit. Other typical psychosis treatments that were common to addiction treatment, including community outreach, pharmacotherapy, and stepwise treatment, may also have helped patients reduce their substance use. Some of the cognitive and motivational deficits associated with schizophrenia may limit the impact of specialized addiction treatments, especially if they are undertaken in group formats or ones with higher expressed emotion that patients with psychosis may not be able to tolerate and thus drop out.

As such, the management of a person with psychosis and addiction may be best approached in a stepwise fashion in which with the initial focus is on management of the acute psychosis. Once stabilized, psycho-education and/or further addiction treatment (relapse prevention, motivational interviewing) may be integrated to reduce substance use and promote abstinence. Finally, consider adding specialized dual diagnosis treatment for patients that do not achieve a significant reduction in substance use by 6-8 weeks of treatment.

REFERENCES:

CONCLUSIONS

Psychosis and SUD frequently co-occur in clinical practice. Although many substance-induced psychotic symptoms will resolve with abstinence alone, some will persist even with abstinence, prompting the need for antipsychotic medication and psychiatric follow-up. The presence of persistent psychotic symptoms despite abstinence, negative symptoms, symptoms in excess of what would be typically expected from a substance, lack of synchrony between substance use and psychotic symptoms, and/or family history of psychosis should prompt the clinician to consider a primary psychotic disorder and treat it early. The evidence to date suggests an advantage of AAPs over CAPs for persons with concurrent psychosis and SUD. The preferred treatment setting is one that primarily addresses the psychosis. Referral to specialized dual diagnosis services and/or assertive community treatment should be considered when there is a lack of progress in substance use behaviour. Ultimately abstinence is desired for best possible treatment outcome, however, given the cognitive impairments often present in psychosis and that psychotic symptoms may limit typical addiction treatment approaches, gradual improvement in function with reduction of substance use may be a more practical goal.
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Variability of QT Interval Measurements in Opioid-Dependent Patients on Methadone

Andrew Worster, MD, Michael Varenbut, MD, Jeff Daiter, MD, Girish M. Nair, MBBS, Carolyn Plater-Zyberk, MSW, Lauren Griffith, PhD, Jihui Ma, PhD, Constantine Zachos, MD, Marco L.A. Sivilotti, MD, MSc

Contact Author:
Andrew Worster, MD
Rm 248 McMaster Clinic, Hamilton General Hospital
237 Barton St. East, Hamilton, Ontario, Canada L8L 2X2
Tel: (905) 521-2100 ext. 75848 Fax: (905) 577-8457
Email: worster@mcmaster.ca

Declaration of Interest: There are no conflicts of interests to report.

Funding/Support: This was an investigator-initiated study with no external funding or support

ABSTRACT

Background: Methadone can prolong the QT interval, a precursor to ventricular dysrhythmias. Measurement of the QT interval can vary with intrinsic and extrinsic factors. Our objective was to assess the agreement and repeatability between different QT interval measurements.

Methods: We recorded ECGs daily for five consecutive days from adults receiving a stable, single daily dose of methadone for opioid dependence. We compared manually measured QT intervals and the calculated QTc intervals to automated measurements.

Results: We obtained 123 ECGs from 26 patients receiving a mean methadone dose of 71 mg/day (range 5 to 240 mg). The manually measured QT intervals from leads II and V5 were similar and consistent (95% limits of agreement -46 to 59 ms), as were the corresponding manual QTc. However, the automated QT reported by the ECG was less consistent (95% limits of agreement -85 to 65 ms), especially at higher QT intervals and at methadone doses over 100 mg/day. Only one of the two subjects at greatest risk for torsades de pointes (TdP) was identified based on the automated QT reading, while six other patients had at least one automated QTc over 480 ms that could not be confirmed on manual measurement.

Conclusions: Accurate identification of QT prolongation in methadone patients is difficult because of intrinsic patient variability in QT length and accuracy of automated measurements. When contemplating ECG screening for this population, these challenges are best overcome with manual and serial QT measurements, especially at doses exceeding 100 mg/day, and interpretation using a QT nomogram to determine risk of ventricular dysrhythmia.

INTRODUCTION

Methadone, a synthetic opioid agonist, has been shown to reduce drug use, crime, risk of HIV transmission, and all-cause mortality, and has transformed the management of opioid addiction.1-12 Increasing attention has been directed at the propensity of methadone to prolong the Q-wave-to-T-wave (QT) interval on the electrocardiogram (ECG) in a dose-dependent fashion.13 This QT interval prolongation represents a delay in repolarization, and is clinically relevant because it allows for the emergence of ventricular tachyarrhythmias such as torsades de pointes (TdP), which can in turn present as syncope or sudden cardiac death. This phenomenon has special implications for patients on methadone maintenance treatment, given their frequent use of other proarrhythmic medications and illicit drugs that also affect repolarization, fragmented healthcare and social supports, and the occasional unexplained sudden death in which methadone-induced dysrhythmia remains implicated. In response, many regulatory bodies including Health Canada and the College of Physicians and Surgeons of Ontario (CPSO) have recommended routine electrocardiographic surveillance of patients prescribed methadone, with substantial implications regarding individualizing dosing and resource allocation in this often marginalized population.14,15 And although an absolute QT or QTc of 500 ms is often considered the threshold of risk of TdP, this likely varies with individuals.14,16

Identifying methadone-induced QT prolongation is difficult because of the challenges in accurately measuring the QT interval.16 Manual measurement of the QT interval is tedious as it is not always clear when the T-wave ends, and it varies with the lead used for the measurement (e.g. lead II vs. V5).16,17 Furthermore, since the QT interval varies inversely with the heart rate, one needs to then calculate the corrected QT interval (QTc) using one of several adjustment formulae. Therefore, the automatically measured QT interval reported by the software imbedded in the electrocardiograph is a much more convenient measure upon which clinicians have come to rely.

Interpreting any clinical measurement, including the QT interval, is ultimately based on understanding its
measurement and variability in the target population of interest, and the significance of changes between individuals and from baseline. Our objectives for this study, therefore, were to measure the QT interval repeatedly in different ECG leads, to calculate the QTc using two different correction formulae, and to compare these to the automated measurements reported by the electrocardiographic software. We sought to characterize the repeatability and agreement between the manual measurements and the automated ones in patients receiving a consistent daily dose of methadone for methadone maintenance therapy.

METHODS

The Research Ethics Board of Hamilton Health Sciences and McMaster University, Hamilton, Ontario, Canada approved this prospective cohort study of adult patients at a single opioid-addiction treatment clinic in the province of Ontario, Canada. All study participants provided written consent, were older than 18 years and met the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria for opioid dependence. Subjects were eligible if considered stable in their recovery as defined by qualifying for two or more take-home doses of methadone each week, and by receiving a consistent daily dose of methadone for a minimum of three days prior to data collection. We excluded from analysis any ECGs obtained following a methadone dose change of more than 5 mg during the five-day data collection period. Subjects provided at least one 30 mL sample of urine under supervision for a urine drug screen for methadone, opiates, and cocaine using qualitative and semi-quantitative homogeneous enzyme immunoassays (iMDx™, NOVX Systems, Markham, ON analyzers). We excluded subjects if they were suspected of urine tampering, or if their urine tested positive for opiates or cocaine, or negative for methadone. We also excluded subjects with known prolonged QT syndrome, a cardiac rhythm device, or evidence of sinus arrhythmia, atrial fibrillation/flutter, intraventricular conduction block, or bigeminy on initial ECG.

We obtained a standard 12-lead digital ECG from each subject daily for five consecutive days using a QRS Universal ECG (DRE, Louisville, KY) at 25 mm/s sweep speed and calibrated at 10 mm/mV amplitude. We recorded all ECGs at the clinic prior to the patient ingesting their daily methadone dose (trough methadone level).

Two investigators, a certified emergency physician and a certified cardiologist with fellowship training in electrophysiology conducted all of the ECG measurements and calculations. Using the ECG software to display the ECG recording on a 15-inch monitor (display resolution 1280 pixels x 1024 pixels), a single investigator (AW) measured three consecutive RR intervals in both leads II and V5 on each ECG. He then identified the beginning of the corresponding QT interval with the software pointer and digital magnifying lamp, and used the “Tangent Method” to identify the end of the QT interval. Using this method, a tangent is drawn to the steepest slope of the last limb of the T-wave and the end of the QT interval is identified when the descending limb of the T-wave returns to the TP baseline when it is not followed by a U wave, or if it is distinct from the following U wave. In keeping with standard practice, we established a priori that when T-wave deflections of equal or near-equal amplitude result in a biphasic T-wave, the QT interval ends at the time of final return to baseline. Also, if a second lower amplitude repolarization wave interrupts the terminal portion of the T-wave and it is uncertain whether the second deflection is a biphasic T-wave or an early-occurring U wave, the termination of the T-wave was to be determined by consensus with a second investigator (GN). This second investigator also independently measured QT and RR intervals on a random selection of approximately 20% of the sample and verified that all measurements agreed to within 5 ms.

We calculated the corresponding QTc intervals using both Bazett’s (QT/√RR in seconds) and Framingham (QT+0.154 (1000-RR in milliseconds)) formulae. We recorded the automated heart rate, QT and QTc readings reported by the ECG software for each ECG. Given a range of thresholds from 450 ms to 500 ms in the literature, we arbitrarily prespecified a QTc cutpoint of 480 ms to compare manual and automated QTc measurements. Finally, we also plotted both the manual and automatic QT intervals against HR on the QT nomogram as proposed by Chan et al. All manual measurements were performed independently on each ECG without knowledge of the measurements from other days and blinded to the automated readings as well as the methadone dose.

To assess the difference between the QT interval durations from lead II and machine, we calculated a sample size of 25 participants with 5 ECGs each would allow 80% power at significance level of 0.05 to identify a minimum difference between the two measurements of 10 ms, assuming
a variance of 15 ms², and the correlation between the repeated measurements for the same patients of 0.60. For our statistical analyses, we used the method of Bland and Altman to determine the repeatability of the manual QT measurements on each ECG, and the agreement between manual measurements on lead II versus lead V5, between manually measured QTc values using Bazett’s versus Framingham correction, and between the manual and automated QT measurements on each ECG. We generated Bland-Altman plots and calculated the bias (i.e. the mean difference between measurement methods), 95% limits of agreements and the repeatability coefficient (i.e. two readings by the same method lie within the repeatability coefficient 95% of the time). We also examined repeatability and agreement between both the manual and automated QTc values within subjects across the 5 days of observation. We performed subject-level random-effects regression analysis adjusting for dose and accounting for the intra-subject correlation to compare the results of the manually measured QT intervals. We also performed a random-effects regression analysis to compare the Bazett’s and Framingham QTc to each other and to the machine measured QTc. Missing values were handled as “last value carried forward” for the purposes of the analysis of agreement. Finally, we studied the influence of methadone dose on the QTc, as well as on the agreements between methods of measuring and calculating QTc.

RESULTS

A total of 26 patients consented to participate. The daily methadone dose for the participants ranged from 5 - 240 mg/day with a mean of 71 mg/day. ECGs were recorded for only four of the five days for 5/26 subjects. One subject whose methadone dose was increased by 15 mg on day 4 had the subsequent two ECGs excluded to leave a total of 123 eligible ECGs for the analyses. The software was unable to provide a QT or QTc in three of these ECGs. Lead I was used instead of lead II for four manual readings, and lead V4 instead of V5 in another because the corresponding T wave was less isoelectric.

On any given ECG, the manually measured QT intervals from either lead II or lead V5 were consistent (bias 6 ms (95% limits of agreement -46 to 59 ms) lead V5 versus II) and repeatable (repeatability coefficients 41.4 and 43.2 ms), irrespective of the average QT or the methadone dose. Bazett’s correction formulae generated a slightly longer QTc compared to the Framingham correction (bias 11.0 ms (s.d. 13.9 ms) Bazett’s vs. Framingham), as expected given the heart rates of subjects (mean 72 bpm (s.d. 13 bpm)). However, the automated QT reported by the software did not agree as well with the manually measured QT (bias -10.2 ms (95% limits of agreement -85 to 65 ms) manual vs. automated). Moreover, the degree of disagreement between manual and automated QT intervals increased at higher QT readings (Figure 1) and also at methadone doses over 100 mg/day (Figure 2). Logarithmic transformation did not appreciably reduce the disagreement at higher QT readings or doses.

The regression analysis, adjusting for dose and between-subject variation, yielded similar results: the manually measured QT interval durations from leads II and V5 were similar (p=0.12), but both were significantly shorter than the automated QT by 10 to 15 ms on average (p=0.05 lead II, and <0.001 lead V5; Table 1). The corresponding calculated QTc intervals are shown in Table 2. The QTc calculated from manual measurements was again about 10 to 25 ms shorter than the automatically reported value. Using Bazett’s formula also resulted in a significantly longer QTc by about 10 to 15 ms compared to the Framingham formula (p=0.005).

When comparing each subject’s serial QTc values over the 5 consecutive days of observation, there was poor repeatability for both manually (repeatability coefficient 114 ms) and automatically (repeatability coefficient 92 ms) obtained intervals.

At the prespecified QTc cutpoint of 480 ms, three subjects (methadone dose range 105 to 130 mg/day) had at least one manual QTc over 480 ms based on the Framingham correction, only one of which had an automated QTc over the same cutpoint. An additional six patients (methadone dose range 45 to 240 mg/day) had at least one automated QTc over 480 ms (Figure 3). When the uncorrected QT was plotted against heart rate on the QT nomogram, one patient (methadone dose 130 mg/day) had the concerning combination of QT over 480 ms and heart rate below 60 per minute identified on both manual and automatic reading of the ECG on multiple days (Figure 4), and one additional subject was also in the “at risk” zone of the nomogram based only on the manual measurement.

DISCUSSION

Several prospective studies have demonstrated a correlation between methadone dose and ECG machine calculated QTc. Three of these studies specify using Bazett’s QTc formula, the most common correction formula used but which also over-estimates the QTc at increased heart rates, thereby exaggerating the significance of methadone effects on the ECG. Another limitation of automated QT interval measurement is that the software may not identify the true end of abnormally shaped T-waves, nor the beginning of a U wave, again

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overestimating the QTc. Sinus arrhythmia, a normal variant in young adults in which there are intermittent prolonged R-wave-to-R-wave (RR) intervals, can also falsely increase QT measurements and QTc calculations. Finally, intrinsic variability, which is the difference in measurements from the same patient resulting from differences in activity level, postural changes, circadian patterns, and food ingestion, has not been measured in methadone patients, and is rarely controlled for. Therefore, without measuring or controlling for the many variables involved in assessing the association between methadone and QT/QTc interval, it becomes impossible to conclude whether changes in the latter are truly due to methadone or some intrinsic variability or measurement source. One approach to reducing the variability in QT and QTc measurements is to ensure all serial ECGs for any given patient are performed under identical circumstances. Another is to collect ECGs via continuous Holter monitoring prior to the initiation of methadone and creating a QT nomogram for each patient.

The challenges to identifying prolonged QT, however, are not limited to intrinsic variability. We found through different analyses that the automated measurements of QT and QTc on average overestimate the manual QT and QTc respectively, as evidenced by a bias. If the automated QT or QTc measurements merely overestimated the true parameters and did so consistently, their value as highly sensitive and convenient screening tests would be affirmed. Unfortunately, we also identified false negative cases (where the automated readings appeared normal while the manual measurements were not) as well as false positives. In three instances the manually measured QT interval was more than 150 ms longer than the QT reported by the electrocardiographic software. As such, the convenience of relying on the automated measurement needs to be weighed against its accuracy.

Our results also show that the discrepancy between the manual and automated measurements increase at higher methadone doses, i.e. the doses that are most likely to prolong the QT, and most notably above 100 mg/day when the concern about prolonged QT becomes greatest.

For those intent on screening MMT patients for QTc prolongation, the challenges then are to obtain the ECG under standardized conditions and manually measure the QT and calculate the QTc at least for those patients at doses over 100mg/day. Plotting the manual QT against the heart rate on a QT nomogram may help with the interpretation, rather than relying on correction formulae. Regardless, we do not endorse relying on the automated QTc reading by itself to make clinical decisions (including dose adjustments or switching to buprenorphine) without manual examination of the ECG. This limitation of the automated software has important implications for methadone maintenance treatment programs and the implementation of the unproven practice of screening in order to prevent cardiac morbidity/mortality in methadone-treated opioid addicts.

There were several limitations with this study. Ideally, we would have recorded each patient’s ECG continuously over 24 hours or at least at Cmax of methadone. However, neither of these options is feasible for screening purposes in the clinical setting. Similarly, we did not test each patient for evidence of hypokalemia, other electrolyte abnormalities, or renal dysfunction. The full impact of possible co-ingestents could not be assessed because of the limitations of urine drug screening. Nor did we record information about other QT-modifying drugs the patients were taking or dose changes of same during the study period. Finally, we did not measure interobserver repeatability of the electrocardiographic measurements.

**CONCLUSIONS**

Accurate identification of QT prolongation in methadone patients is difficult because of intrinsic patient variability in QT length and accuracy of automated measurements. These challenges are best overcome with manual and serial QT measurements, especially at doses exceeding 100 mg/day, and interpretation using a QT nomogram to determine the risk of ventricular dysrhythmia.
REFERENCES


FIGURE 1.

Each of four possible QTc intervals derived from manual measurement (lead II or V5, and two different correction formulae) from each daily ECG is shown plotted against the automatic QTc reported by the ECG machine software, with the main diagonal of perfect agreement shown as a dashed line. The prespecified cutpoint of 480 ms is also indicated illustrating the discordant pairs: “falsely positive” automated QTc readings in the lower right quadrant, and “falsely negative” in the upper left.

FIGURE 2.

Bland-Altman plot showing the agreement between a manually measured QT (average of leads II and V5) and the automated QT reported by the ECG machine software for each daily ECG.
### TABLE 1

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<th>Std Dev*</th>
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<tr>
<td>Lead V5**</td>
<td>401.65</td>
<td>59.18</td>
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<td>Machine</td>
<td>409.16</td>
<td>45.61</td>
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*Std Dev = standard deviation;  
** Manual measurements with digital calipers.

### TABLE 2

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<td>29.69</td>
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*Std Dev = standard deviation;  
**Range = difference between the maximum and minimum measurements.

### FIGURE 3.

The manually measured QTc (filled diamonds; Framingham correction, average of leads II and V5) and the automated QTc (open triangles) reported by the ECG machine is shown against the daily methadone dose for each daily ECG. The dashed line denotes the cutpoint proposed by some to alert to the increased risk of torsades de pointes and sudden death.

### FIGURE 4.

QT Nomogram: The manually measured QT (measured in triplicate in lead II) plotted against heart rate as proposed by Chan et al (Chan A, Ishbister GK, Kirkpatrick CM, Dufful SB. Drug-induced QT prolongation and torsades de pointes: evaluation of a QT nomogram. QJM. 2007;100(10):609-15.) for each daily ECG. Subjects taking 100 mg/day or more of methadone are shown as filled diamonds. QT intervals longer than the dashed line are at increased risk of torsades de pointes at a given heart rate.
Methadone and QTc screening: Weighing the risks and benefits

Seonaid Nolan1, Evan Wood1, 2
1British Columbia Centre for Excellence in HIV/AIDS, St. Paul’s Hospital, Vancouver, Canada
2Department of Medicine, Faculty of Medicine, University of British Columbia, Vancouver, Canada

Send correspondence to:
Seonaid Nolan, MB BCh, FRCPC
BC Centre for Excellence in HIV/AIDS
608 - 1081 Burrard Street, Vancouver BC V6Z 1Y6 CANADA
Tel: 604-682-2344 ext 66373
Fax: 604-806-9044
Email: seonaidn@gmail.com

COMMENT

While methadone therapy remains the gold standard for the pharmacological treatment of opioid dependence, certain concerns related to its side effect profile are long-standing. Under heavy scrutiny has been the association between methadone use, prolongation of the corrected QT (QTc) interval on the electrocardiogram (ECG) and the risk of subsequent development of a life-threatening cardiac arrhythmia (most notably torsade de pointes or TdP)1. Methadone’s role in QTc prolongation has previously been described2-4. Through cardiac myocyte calcium channel blockade and its inhibitory action on voltage gated potassium channels, the opportunity for interrupted ventricular repolarization exists, which can manifest on the ECG as a prolonged QTc 5, 6. Previous literature demonstrates an increase in the QTc can occur during methadone initiation7-9, with increased methadone doses1, 2, 9-10 and that normalization of this interval can occur with either discontinuation of methadone or a dose reduction11-13. Despite the potential for methadone to prolong the QTc, it is important to note that the occurrence of any prolonged QTc is not an inherent danger. Rather, a QTc of 500 milliseconds or greater tends to be the accepted cut-off for the increased risk thought to be related to the development of TdP or sudden cardiac death (SCD)14, 15. Approximately 2% to 16% of patients on methadone maintenance therapy are estimated to exceed this threshold14-16. While cases of methadone use and the development of TdP or SCD have previously been reported14-16, the evidence is extremely limited14 and does not control for other factors known to contribute to a prolonged QTc (ie. electrolyte abnormalities, structural heart disease, other medications or illicit drugs)17. Importantly, causes of sudden cardiac death attributable to illicit drug use are an important confounder among this population21, 22, and the relative risks of under-treated heroin use versus the theoretical risk of methadone on QTc have not been established.

Current Canadian screening guidelines generally recommend that all patients on a daily methadone dose of 150mg or more or those with QTc prolonging risk factors be screened with an ECG at baseline and after any change in clinical status23, 24. The evidence upon which these recommendations are based, however, is less clear. A recent Cochrane review reported not only a distinct lack of evidence to support the use of routine ECG screening for methadone treated patients but also stated it was not possible to draw any conclusions about the effectiveness of such a practice for preventing cardiac arrhythmias or sudden cardiac death19. While these conclusions do not rule out the possibility that screening may have a benefit, this review highlighted a notable absence of previous studies detailing the actual efficacy of QTc screening in preventing such adverse outcomes19.

In this issue of the Canadian Journal of Addiction, Worster et al examined the accuracy and repeatability of QTc screening among 26 patients on a stable methadone dose for opioid dependence and had 5 consecutive daily ECG’s recorded. Overall, there was poor repeatability when comparing each subject’s serial QTc values (repeatability coefficient for manual and automated measurements 114ms and 92ms respectively)25. Furthermore, discrepancy was noted in the reported QTc value depending on which technique (manual vs automated) and/or correction formula (Bazett’s vs Framingham) was utilized. This study clearly demonstrates the technical challenges and variability involved in what is often considered an uncomplicated screening procedure and highlights the inaccuracy in risk stratifying patients based on a single ECG recording. Additionally, with the multitude of fluctuating intrinsic and extrinsic patient factors which may also play a role (ie. electrolyte disturbances, metabolic disorders, medications, illicit drug use, structural heart
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Mortality risk associated with methadone-induced TdP

Thus, to accurately appreciate the significance of the mortality risk associated with methadone-induced TdP or SCD, it should be compared against the known risk of morbidity and mortality associated with untreated opioid addiction. While existing data should be viewed with some skepticism given the inability to accurately ascertain causes of death in this population, the mortality of methadone-induced TdP has been estimated at 0.06 deaths per 100 patient years whereas that associated with untreated heroin dependence is approximately 1 to 3 deaths per 100 person years. Furthermore, amongst opioid-dependent patients, methadone therapy has been shown to reduce mortality risk by 2 to 11 times.

There has been longstanding uncertainty regarding the utility and effectiveness of ECG screening for methadone initiation or maintenance therapy for opioid dependence. The paper by Worster and colleagues further clouds this issue by highlighting that the accuracy and reproducibility of QTc measurement must itself now be questioned. In this context, until further research can validate the utility of routine ECG screening, we recommend against its use unless clinicians feel that a change in the methadone regimen would pose a lower risk than the theoretical risk of a potentially prolonged QTc.

REFERENCES


CSAM-SMCA Certification is valid for 10 years\(^1\).

Members obtain certification by fulfilling the following criteria:

1. Hold a medical license from Canada or the US that is in good standing with the licensing authority.
2. Successful completion of the American Society of Addiction Medicine (ASAM) examination/American Board of Addiction Medicine (ABAM) or the International Society of Addiction Medicine (ISAM) examination.
3. Successful completion of postgraduate medical training with certification\(^2\) from one of the following three:
   - Professional Corporation of Physicians of Quebec
   - Royal College of Physicians and Surgeons of Canada
   - College of Family Physicians of Canada
4. Current membership in the Canadian Society of Addiction Medicine (Certificants may consent to have their names on the CSAM-SMCA webpage)
5. CSAM-SMCA Certificants will adhere to the following requirements for the duration of CSAM-SMCA certification:
   a. membership (i.e. status as good-standing) in the Canadian Society of Addiction Medicine and
   b. participation in CSAM-related activities\(^3\) and/or other efforts to advance the field of addiction medicine in Canada (if the latter, please provide details with application)

\(^1\) CSAM certification is not time limited for physicians having the “grandfather” provision within ABAM/ASAM.
\(^2\) Physicians interested in CSAM Certification and for whom criteria #3 cannot be satisfied, should contact CSAM directly.
\(^3\) Activities such as participation in CSAM committee work and related activities (e.g., annual conference) would qualify.
The 15th Annual ISAM meeting in Kuala Lumpur (Malaysia) – Selected Abstracts

The 15th International Society of Addiction Medicine [ISAM] meeting attracted some 500 attendants from 50 countries. Canada was very well represented and CSAM-SMCA has a Category I affiliation with ISAM, and as such we are able to select abstracts of relevance to Canada for publication in our Journal.

The following selection reflects the breadth and depth of the meeting.

See you all in Yokohama, Japan for the 16th ISAM meeting Oct 2-6, 2014 and the 17th ISAM meeting in Dundee, Scotland Oct 4-8, 2015.

The Editor

A. BUILDING EVIDENCE

TRANSLATING EVIDENCE INTO THE BEST OUTCOMES IN ADDICTION TREATMENT
Robert Ali, Linda Gowing (Australia)

The rationale for the recent emphasis on evidence-based practice stems from a belief that clinical decision-making informed by experimental studies should improve the overall quality of treatment, facilitate consistent practice, increase (cost) effectiveness, and improve service providers accountability. Significant national effort in the United Kingdom through NICE have resulted in guidelines for psychological care while international efforts through UNODC’s TreatNet have developed training resources. In the US, technology transfer utilizing a clinical node approach through NIDA’s Clinical Trials Network is shaping practice. Each approach attempts to blend research evidence, clinical experience and patient expectations. In Australia, the National Policy and Guidelines for Medication-Assisted Treatment of Opioid Dependence is under development. The document intends to provide a broad policy context and a framework for medication-assisted treatment of opioid dependence as well as clinical guidelines on approaches involving the use of methadone, buprenorphine or naltrexone. The primary audience is the non-specialist prescriber, with the evidence grade based upon the strength of evidence. The consultation process during their development has highlighted significant areas of disagreement where the evidence base poor are the subject of ongoing consultation. This presentation will review the process undertaken during the guidelines development and discuss the implications for future practice.

INTRODUCTION TO COCHRANE: WHERE DOES ADDICTION FIT?
Robert Ali (Australia)

The Cochrane collaboration was founded in 1993 to undertake systematic reviews. The Collaboration was established to identify appraise and synthesize empirical evidence from randomized controlled trials and case-controlled trials to answer predefined research questions. The collaboration now involved around 28,000 people from over a hundred countries. The Cochrane Drug and Alcohol Group was formed in 1998. The group oversees systematic reviews of the prevention, treatment and rehabilitation of problematic substance use. During its lifetime there have been 63 reviews undertaken which considered nearly 3000 studies for inclusion of which 30% were deemed to be of sufficient quality to be included. This talk will summarize where the group fits within the Cochrane approach and provide guidance on how the collaboration can assist informing clinical decisions.

B. A NEUROBIOLOGY UPDATE

THE ROLES OF NEUROBIOLOGY IN REDEFINING TREATMENT FOR ADDICTION
Eliot L. Gardner (USA)

Addiction derives from drug action on the reward/pleasure circuits of the brain – producing the “high” that addicts seek. The reward circuitry links the ventral tegmental area, nucleus accumbens, and ventral pallidum via the medial forebrain bundle. The dopaminergic component in this circuitry is the crucial addictive-drug-sensitive component. Drug self-administration is done to keep nucleus accumbens dopamine within an elevated range to maintain elevated hedonic tone. The brain circuits mediating the pleasurable effects of addictive drugs are different from those mediating
physical dependence, and from those mediating craving and relapse. There are important genetic variations in vulnerability to drug addiction, but environmental factors such as stress and social defeat also alter brain-reward mechanisms so as to impart addiction vulnerability. Addiction correlates with hypodopaminergic dysfunction within the reward circuitry of the brain. Serotonergic, opioid, endocannabinoid, GABAergic and glutamatergic mechanisms also play roles in addiction. Drug addiction progresses from occasional recreational use to impulsive use to habitual compulsive use. This correlates with a progression from reward-driven to habit-driven drug-seeking behavior, and correlates with a neuroanatomical progression from ventral striatal (nucleus accumbens) to dorsal striatal control over drug-seeking behavior. The three classical sets of craving and relapse triggers are (a) re-exposure to addictive drugs, (b) stress, and (c) re-exposure to environmental cues (“people, places, things”) previously associated with drug-taking behavior. Drug-triggered relapse involves the nucleus accumbens and the neurotransmitter dopamine. Stress-triggered relapse involves (a) the central nucleus of the amygdala, the bed nucleus of the stria terminalis, and the neurotransmitter CRF, and (b) the brain-stem lateral tegmental nucleus and the neurotransmitter norepinephrine. Cue-triggered relapse involves the basolateral nucleus of the amygdala, the hippocampus, and the neurotransmitter glutamate. Knowledge of the neuroanatomy, neurophysiology, neurochemistry and neuropharmacology of addictive drug action in the brain is currently redefining the treatment of drug addiction.

CUTIC NICO TINIC RECEPTOR EFFECTS ON COGNITIVE PERFORMANCE IN NON-SMOKERS WITH AND WITHOUT SCHIZOPHRENIA
Sungwon Roh, Susanne S. Hoeppner, Catherine A. Fullerton, Luke E. Stoeckel, A. Eden Evins (USA)

Rationale: Dysregulation of neuronal nicotinic acetylcholine receptors (nAChRs) has been implicated in the pathophysiology of cognitive deficits in schizophrenia. Nicotine enhances cognitive performance in the domains of attention and memory in healthy volunteers and perhaps to a greater extent in people with schizophrenia, while deficits in attention are associated with failure to quit smoking in those with schizophrenia. Objectives: This study aimed to investigate the acute effects of a nAChR antagonist, mecamylamine, and a nAChR agonist and partial agonist, varenicline, on attention, working memory and response inhibition in non-smokers with and without schizophrenia. Methods: Single, oral doses of mecamylamine, 10 mg, varenicline, 1 mg, and placebo were administered, one week apart, in random order to adults with schizophrenia (n=30) and to healthy volunteers with no lifetime Axis I psychiatric illness (n=41) in a double-blind, crossover design. Participants were non-smokers in order to avoid confounding effects of nicotine withdrawal and reinstatement on cognitive performance. The primary outcome of interest was sustained attention as assessed with hit reaction time (HRT) variability on the identical pairs continuous performance test (CPT-IP). Results: There was a consistent main effect of treatment such that performance on mecamylamine was worse than performance on varenicline in both groups while neither differed from placebo on many measures, including CPT-IP HRT variability at all levels of task difficulty. There was a treatment by diagnosis interaction such that the performance of participants with schizophrenia on mecamylamine was worse than on varenicline or on placebo on CPT-IP 2-digit HRT, 3-digit random errors, and 4-digit hit rate, an effect not observed in healthy volunteers. Conclusions: These findings support a role for nAChR’s in attention and memory, and in the pathophysiology of cognitive dysfunction in schizophrenia, and suggest that those with schizophrenia may be particularly sensitive to nAChR blockade.

C. NATIONAL POLICIES

UNDERSTANDING SWISS DRUG POLICY CHANGE AND THE INTRODUCTION OF HEROIN MAINTENANCE TREATMENT
Riaz Khan, Yasser Khazaal, Gabriel Thorens, Daniele Zullino, Ambros Uchtenhagen (Switzerland)

Background: Switzerland’s political will and the pragmatic approach towards, its national drug policy instilled a paradigm shift for exploration, innovation and scientific documentation in the medical prescription of diacetylmorphine heroin). Aims: The aim of this paper is to illustrate how, a basically conservative country like Switzerland was able to play such a pioneering role in the field of addiction treatment and in creating a drug policy which includes the medical prescription of heroin, as part of the
Aims/Methods: Efficacy, its predictors and safety were tested in a 6-month, double-blind RCT with XR-NTX given IM every 28 days with outpatient counseling, following detoxification at 13 Russian sites. Long-term effectiveness was then determined in both the randomized XR-NTX patients who continued on XR-NTX, plus in the original placebo (PBO) patients who were switched to open-label XR-NTX, over a 1-year extension. Findings: The 6-month RCT showed significantly superior XR-NTX (n=126) outcomes vs. PBO (n=124) in: decreased opioid use, reduced opioid cravings, prevention of relapse to physical opioid dependence (PBO:XR-NTX=17:1), and retention, with no overdoses, no deaths and similar discontinuation rates (2% in both groups due to adverse events (AEs), 0% due to severe AEs). No significant interactions of baseline characteristics-by-treatment-group predicted abstinence or retention, suggesting that XR-NTX benefits were similar regardless of patient severity. In the 1-year extension (n=114; 67 XR-NTXXR-NTX; 47 PBOXR-NTX), 62.3% (95% CI: 45.4%, 70.2%) completed. Urines indicated that 50.9% were opioid abstinent throughout. AEs reported by 21.1% of patients were judged to be study drug related. Injection site reactions were infrequent (6.1%) and the majority were mild. Liver function elevations occurred in 16.7%; none were judged clinically significant. No patients died, overdosed or discontinued due to severe adverse events. Limitations include the open-label design of the extension study, and the need for replication, larger samples and determination of generalizability beyond Russia. Conclusions: Data from the double-blind study established the efficacy and safety of XR-NTX for prevention of relapse to opioid dependence following detoxification. Further analyses showed a broad effect across a range of clinically relevant patient variables. No deaths or serious overdoses were reported. Hepatic safety was confirmed, even in patients with stable chronic Hepatitis C and HIV. The extension study showed long-term effectiveness over an additional year of XT-NTX with no new safety signals.

INJECTABLE EXTENDED-RELEASE NALTREXONE (XR-NTX) FOR PREVENTING RELAPSE TO OPIOID DEPENDENCE: 14 STUDIES IN U.S. POPULATIONS & SETTINGS

DR Gastfriend, J Zummo (USA)

Aim: To examine once-monthly injectable XR-NTX data from studies across the USA, in outpatient and residential settings, in varying populations, and in criminal justice environments. Methods: All 14 known published, in press or presented clinical studies of intramuscular XR-NTX formulations for opioid dependence (aggregate XR-NTX-treated N=1,046) were examined for data on efficacy, effectiveness and health economic outcomes. Results: Findings include: effectiveness for maintaining abstinence, retention, decreasing craving and preventing relapse for study durations as long as 24 months, including feasibility in recovering health professionals, commercially insured/employed patients and uninsured/public populations. Reports show promising effectiveness in community outpatient, residential and drug court, jail and parole settings. Results are consistent regardless of whether sponsored by the manufacturer vs. independent. Data indicate good generalizability of findings and the applicability of the agent both in settings that have and do not have opioid substitution treatment. Safety and tolerability have been shown, without intractable acute pain, overdose or death rates, and no new safety signals were observed. Health economic analysis shows
cost effectiveness vs. oral agents, owing to decreased hospital utilization with XR-NTX. Conclusions: XR-NTX is a pharmacologic approach to opioid dependence treatment that, with psychosocial treatment, has been shown to provide consistent and durable in-treatment effects across differing populations, treatment systems and financing models. Limitations include the need for more controlled and randomized designs, and for data regarding post-completion outcomes, detoxification and induction; protocols that address the latter require study. While more research is needed, a three decade-long goal of an extended antagonist formulation is yielding a promising therapy and a policy opportunity.

PATIENT PERSISTENCE WITH BUPRENORPHINE/NALOXONE FILM AND TABLET FORMULATIONS IN THE TREATMENT OF OPIOID DEPENDENCE IN THE UNITED STATES: RESULTS FROM A 2010-2012 PRIVATELY INSURED RETROSPECTIVE DATABASE

Clay, E (USA), Khemiri, A (France), Ruby J (USA), Aballea, S (USA), Zah, V (Canada)

BACKGROUND: Since September 2010, the buprenorphine/naloxone combination (BUP/NAL) has been available in a film formulation for the treatment of opioid dependence. OBJECTIVE: US National insurance claims data were analyzed to compare patient persistence and healthcare charges between the two formulations: film and tablet. METHODS: A retrospective cohort analysis was performed using medical claim records extracted from the Invision DataMart database from September 2010 to June 2012. Patients initiating treatment with BUP/NAL after the launch of film (September 2010) were classified in two groups according to formulation of initial prescription: film or tablet. Time to treatment discontinuation and monthly healthcare charges by treatment phase (before treatment, initiation period, during treatment, discontinuation period, after discontinuation and reinitiation period) were compared between the two groups, adjusting on baseline characteristics (demographics, comorbidities, treatment, and resource utilization before treatment). RESULTS: The analysis over the period from September 2010 to May 2012 included over 1500 patients initially treated with each comparator (film, tablet), followed over 18 months on average. Of those treated with tablet, 13.20% of patients switched to film. The proportion of patients persistent at 6 months was higher in the film group than in the tablet group (58.46% vs. 63.26%; p=0.03). The hazard ratio for treatment discontinuation with film vs. tablet, adjusted on baseline characteristics, was 0.83 (p=0.02). Estimated total charges over 12 months after treatment initiation were $47,334 for patients treated with tablet and lower by 34% (p=0.005) for patients treated with film after adjustment on baseline characteristics. CONCLUSIONS: Patients treated with BUP/NAL film appear to have a lower probability of early treatment discontinuation. Treatment with the film formulation may generate employer / private insurer savings in charges, since charges around discontinuation are relatively high, and charges after treatment discontinuation were found to be lower among patient previously treated with film.

BUPRENORPHINE/NALOXONE FILM IMPLEMENTATION IN AUSTRALIA: THE NORTHERN SYDNEY LOCAL HEALTH DISTRICT EXPERIENCE

Glenys Dore and Mark Hardy (Australia)

Over the course of the last 2 years in Australia, Buprenorphine/Naloxone sublingual tablets have been phased out and replaced by equal dose preparations in a muco-adhesive film. Whilst the pharmacological properties of the two agents are virtually identical, changing clients from tablets to film has been met with a number of challenges to overcome. These include patient's personal resistance to change, based on conservatism or suspicions surrounding new preparations. Northern Sydney Local Health District (NSLHD) is bound by Sydney Harbour to the south and the Hawkesbury River to the north. It serves over 80000 people, which is more than 11% of the population of New South Wales. As Clinical Director, based at Royal North Shore Hospital, Dr Dore oversaw the implementation of this new formulation of Buprenorphine/Naloxone in all the opioid substitution clinics within the network. In order to address the change in preparation, structures were put in place, wherein patients were offered counselling, cognitive therapeutic approaches, psychoeducation, staff training and support to assist in the change from one preparation to another. Overall, acceptance of the change in preparation was virtually universal. The change to Buprenorphine/Naloxone film afforded some previously unrecognized opportunities; where patients maintained on other forms of Medication Assisted Treatment (MAT)
were identified and offered transfer to the film. Among these, all patients on buprenorphine mono preparation (except where contra-indicated) as well as a number of clients on methadone took the opportunity to transfer to the combination film. This presentation explores how the service met the challenge of the change in preparation, emphasising the support and structures put in place to assist patients in the changeover. Brief discussion regarding transfer from buprenorphine mono and methadone will also be covered.

**SALOME : STUDY TO ASSESS LONGER-TERM OPIOID MEDICATION EFFECTIVENESS: A PROGRESS REPORT**

Suzanne Brissette, Kirsten Marchand, Eugenia Oveido-Joeckes, Martin Schechter, Michael Krausz (Canada)

Introduction : During the North American Opiate Medication Initiative (NAOMI) trial, in which the efficacy of injectable heroin (or diacetylmorphine, DAM) was compared to that of oral methadone, injectable hydromorphone (HM) was administered to a small number of participants for methodological purposes. Interestingly, it showed similar treatment effectiveness when compared to DAM. However, the study was neither designed nor powered to evaluate HM’s efficacy. Description: The SALOME study, currently ongoing, was specifically designed to test HM’s efficacy as compared to DAM, both in injectable and oral forms. During phase I, participants are randomized to receive either injectable DAM or injectable HM in a double blind fashion. After 6 months of injectable treatment, each group is then re-randomized into either the injectable or oral formulation of the drug they received in phase I. Again, the double blind is maintained with regard to the study medication. This design will not only allow comparisons of HM to DAM but also comparisons of oral to injectable formulations. Results: As of May 2013, 131 participants have been recruited and randomized into phase I. Of those, 89 have been randomized to phase II, 44 in the oral arm and 45 in the injectable arm. Since the SALOME protocol is still underway, no outcomes data is available. However, retention in treatment is an inclusion criteria for phase II: six months retention in phase I is currently 92%. A brief summary of the NAOMI study will be discussed with regards to the HM data.

**IMPRISONMENT AMONG OPIATE DEPENDENT PATIENTS ON COMMUNITY BASED MEDICATION - ASSISTED TREATMENT**

Norsiah Ali, Suzaily Wahab, Mahmud Mazlan, Mohd Alif (Malaysia)

Introduction: Chronic untreated drug dependence is likely to result in high rates of repeated contacts with the criminal justice system. Malaysia has started free Medication-Assisted Therapy (MAT) for opiate dependent since 2005. This study evaluates the MAT program in a government health clinic in terms of retention rate and imprisonment before & after joining treatment program. Method: Retrospective evaluation of samples in Methadone Maintenance Therapy (MMT) who has been on registered for at least 3 years in Tampin Health Clinic, Malaysia (Nov 2006 - May 2010). Number of detainment due to drug related offence after joining treatment program was analyzed and compared to before on treatment. Result: A total of 165 samples were identified. Their mean methadone dose in maintenance phase was 38.4mg (min: 0 mg, max: 90 mg, and mean duration in treatment was 54.21 months (min: 1 mth max: 77 mths, SD 21.15 mths). It was found that 76.9% (N=130) were still in treatment program, 5.3% (N=9) drop out due to arrested by police and imprisoned, 5.9% (N=10) defaulted, 1.2% (N=2) were terminated from treatment due to aggression and 8.3% (N=14) had died. There was significant reduction in number of imprisonment after joining MMT. The median number of imprisonment before on MMT was 2.00 (IQR 1.00-4.00) and the median number of imprisonment after joining MMT was 0.00 (IQR 0.00 -0.00 ). Wilcoxon Signed Ranks Test was significant ($z$: -9.79, $P< 0.0001$). Conclusion: This study found that Medication-Assisted Therapy using methadone conducted in a primary care clinic using methadone was successful in reducing number of imprisonment.

**PHARMACEUTICAL DRUG MISUSE: NEW CHALLENGES FOR ADDICTION MEDICINE**

Nick Linteris (Australia)

Pharmaceutical drug misuse is becoming an increasing area of concern internationally, challenging many traditional clinical, research and policy approaches in the D&A field. There has been a marked expansion in the use of pharmaceutical opioids, tranquillisers and stimulants in many ‘Western’ countries such as USA, Canada and Australia, accompanied by increased levels of related harms. There is also evidence of increased use and misuse of particular medications, such as tramadol, in a number of European, Asian and African countries. However
traditional D&A frameworks that have developed to respond to alcohol and illicit drugs do not adequately address the complex issues that relate to pharmaceutical drug misuse. This paper will examine implications for clinicians, researchers and policy makers in addressing pharmaceutical drug misuse, with particular emphasis upon the leadership role of Addiction Medicine in this emerging field.

E. ALCOHOL/ALCOHOLISM

ARE THERE ANY BENEFITS FROM REDUCING ALCOHOL CONSUMPTION?
Hannu Alho (Finland)

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 (Rehm 2013). Several examples demonstrate that total alcohol consumption has a significant impact on chronic consequences of excessive drinking, such as mortality from liver cirrhosis. However, many treatment programs promote abstinence as the only/main acceptable treatment goal for patients with an alcohol use disorder. 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-V 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 a clear opportunity to address patient heterogeneity and lower the treatment threshold by bringing new patients into the treatment.

ACCEPTANCE OF CONTROLLED DRINKING AS A TREATMENT GOAL OF ALCOHOL DEPENDENCE: CURRENT CONDITIONS IN JAPAN
Tsuyoshi Takimura, Hitoshi Maesato, Hideki Nakayama, Hiroyuki Sakuma, Atsushi Yoshimura, Tomomi Tobiyama, Mitsuru Kimura, Sachio Matsushita, Susumu Higuchi (Japan)

Aims: Although abstinence has been traditionally viewed as the optimal treatment goal for alcohol dependence (AD) in Japan, the need for harm reduction approaches that target a reduction in alcohol consumption has been recognized. We conducted two surveys among treatment specialists of AD and in actual clinical settings to investigate whether controlled drinking (CD) is an acceptable treatment goal in Japan. Methods: In the first survey, a mailed questionnaire was sent to 270 physicians specializing in the treatment of AD to evaluate the acceptance of CD as a treatment goal, the definition of CD, the reasons for accepting or rejecting CD, and the patient factors used to make treatment-goal decisions. In the second survey, the applicability of CD as a treatment goal for patients with AD who had been examined for the first time by psychiatrists at three specialized treatment hospitals was examined. Results: The first survey revealed that CD as an interim goal on the path to abstinence was accepted by about two-thirds of the specialists, while CD as a final goal was accepted by about one-third of the specialists. Specialists who accepted CD relied mostly on factors such as the severity of dependence, the attitude toward CD and abstinence, and the level of psychological dependence and social stability when making treatment-goal decisions. In the second survey, the applicability of CD as a treatment goal for patients with AD who had been examined for the first time by psychiatrists at three specialized treatment hospitals was examined. Conclusions: CD was accepted as an interim goal by about two-thirds of the specialists, while CD as a final goal was accepted by about one-third of the specialists. Specialists who accepted CD relied mostly on factors such as the severity of dependence, the attitude toward CD and abstinence, and the level of psychological dependence and social stability when making treatment-goal decisions. The second study showed that physicians judged CD to be applicable as an interim or a final goal for 25% of the patients with AD who sought treatment at outpatient clinics. Conclusions: CD was accepted as an interim goal by two-thirds and as a final goal by one-third of Japanese physicians specializing in AD. Furthermore, CD was judged by specialists to be a reasonable interim or final goal in 25% of actual alcoholic patients in Japan.

SAFETY GUIDELINES: DISULFIRAM ADMINISTRATION
Alharbi, Fares F (Saudi Arabia) and el-Guebaly, Nady (Canada)

Objectives: Disulfiram (DSF) treatment remains a viable option as a treatment for alcohol dependence. There have
been concerns about its safety, which are often used as a reason for withdrawing the treatment or as an argument against starting it. How safe is the current prescription of DSF? This paper aims to provide an update of DSF’s safety-related research. Method: A systematic review of the recent literature was drawn from a comprehensive MEDLINE (2000 to 2012) search. Case reports and clinical trials using DSF for the treatment of alcohol and/or cocaine use and/or dependence were reviewed. Result: Within the specified period, there have been 30 case reports and 8 clinical trials regarding DSF’s side effects. One was a longer trial of DSF spanning >50 weeks. The case reports were related to neurological, hepatic, cardiac, dermatological, psychiatric adverse events, neuroimaging findings, and drug-drug interaction. Because of exclusion criteria, adverse events in DSF randomized double-blind clinical trials seem to be less serious and less frequent than adverse events reported post-marketing. Conclusions: With the safety recommendations in place, we consider the administration of DSF to be safe practice and within an acceptable risk profile.

CULTURE AND ALCOHOLISM
Sung-Gon Kim, Woo-Young Jung (Korea)

Many Korean people under stress try to relieve the stress by eating spicy (hot) food, which is very popular, and they enjoy it even though it causes pain. Furthermore, it is thought that spicy foods have an addictive tendency. Based on these assumptions, we found that subcutaneous administration of capsaicin significantly increased pro-opiomelanocortin mRNA expression in the rat brain (n=10) and concluded that spicy food could increase activity of the central opioid system. (p=0.001). On the other hand, many previous studies have found that alcohol drinking increases neuronal opioid activity in the brain. Therefore, we investigated whether drinking behavior is associated with a preference for spicy food. Our results showed that subcutaneous administration of capsaicin in C57BL/6 mice (n=5 vs 6) decreased alcohol intake significantly in an animal study (p=0.026). In addition, we found that those who had dependence on alcohol (n=190) preferred spicy food more than that of normal control subjects (n=97) in a human study (p=0.008), and found that naltrexone significantly decreased the stimulative effect from acute alcohol drinking in a group of social drinkers with preference for spicy food (n=13) (p=0.001) but not in a group with no preference for spicy food (n=13) in another human study. Therefore, it is assumed that preference for spicy food affects not only alcohol drinking behavior but also the treatment response when treating alcoholism. It is suggested that the central opioid neuronal systems are involved in these relationships.

PATIENT EDUCATION TO ENHANCE 12-STEP GROUP INVOLVEMENT AMONG PATIENTS UNDERGOING DETOXIFICATION: A RANDOMIZED CONTROLLED TRIAL
Vederhus, J.K; Timko, C.; Kristensen, Ø.; Hjemdahl, B.; Clausen, T. (Norway)

Aims: To compare an educational intervention (EI) focused on increasing involvement in twelve-step groups (TSGs; e.g., Alcoholics Anonymous) versus brief advice (BA) to attend TSGs. Design: Patients were randomly assigned to either EI and BA conditions, and followed up at six months after discharge. Setting and Participants: One-hundred and forty substance use disorder (SUD) patients undergoing inpatient detoxification (detox) in Norway. Measurements: The primary outcome was TSG affiliation measured with the Alcoholics Anonymous Affiliation Scale (AAAS), which combines meeting attendance and TSG involvement. Substance use and problem severity were also measured. Findings: At six months after treatment, compared to the BA group, the EI group had higher TSG affiliation (0.91 point higher AAAS score; 95% CI, 0.04 to 1.78; P = 0.041). The EI group reported 3.5 fewer days of alcohol use (2.1 versus 5.6 days; 95% CI, -6.5 to -0.6; P = 0.020) and 4.0 fewer days of drug use (3.8 versus 7.8 days; 95% CI, -7.5 to -0.4; P = 0.028); however, abstinence rates and severity scores did not differ between conditions. Analyses controlling for duration of inpatient treatment did not alter the results. Conclusions: Educational intervention in an inpatient detox ward was more successful than brief advice in terms of patient engagement in 12-step groups at six months after discharge. The educational intervention also reduced substance use. These findings indicate a potential benefit of adding a maintenance-focused element to standard detox.

VALIDATION OF THE ALCOHOL, SMOKING AND SUBSTANCE INVOLVEMENT SCREENING TEST (ASSIST) IN THE ELDERLY
Zullino, D.; Khazaal, Y; Broers, B.; Thorens, G.; Khan, R. (Switzerland)

Notwithstanding its public health impact, the screening of substance use disorders among the elderly is often omitted in clinical settings. The aim of the present study was to test the validity of the ASSIST in a sample of elderly people attending geriatric outpatient facilities (primary care or psychiatric facilities). METHODS: One hundred participants (77.8 \( \pm \) 7.5 y) were recruited in the University Hospitals of Geneva between January 2010 and June 2010. Participants completed the following
assessments: the French version of the ASSIST V3.0, the Addiction severity index (ASI), the AUDIT, the Revised Fagerstrom Tolerance Questionnaire, and the Mini-International Neuropsychiatric Interview (MINIPlus).

RESULTS: The ASSIST showed a good internal consistency for the Global continuum substance risk score or the total substance involvement score (TSI) with a Cronbach’s coefficient of 0.72 (95% CI [0.63, 0.79], p<0.0005). Moreover, ASSIST scores for alcohol, tobacco and sedatives also showed moderate to good internal consistency (0.66, 0.74 and 0.89 respectively). ASSIST scores for alcohol had large positive correlations with the ASI and the AUDIT scores: (r=0.73 and p<0.0005; r=0.8 and p<0.0005 respectively). Conclusions: The results of this study indicate that the French version of the ASSIST is an acceptable and valid screening test for substance abuse and dependence in elderly patients in general and psychiatric elderly health care settings.

F. BEHAVIORAL ADDICTIONS

INTERNET GAMING ADDICTION: A NOVEL TREATMENT APPROACH, THE LINDBERG & BOWDEN-JONES MODEL

A. Lindberg (United Kingdom) and H. Bowden-Jones

The presentation will outline a novel approach in the treatment of Internet Gaming Addiction. The presenters have been delivering treatment at the National Problem Gambling Clinic in the UK for the past 6 years using a Cognitive Behavioural treatment model to treat the 700 pathological gambling referrals per year to the clinic. The success of the treatment and the widening of their expertise has led the duo to widen their sphere of interest to include Internet Gaming Addiction and to develop a treatment programme of 6 basic sessions and 2 follow up sessions which is largely based on the Self-Regulatory Executive functioning model, developed by Prof. Adrian Wells. His theory has been widely established in the literature in association with a number of mental health conditions and also alcohol dependency and problem gambling. It has however never, until now, applied to Internet Gaming Addiction. The main aspects of treatment are focused on: Increasing psychological and attentional flexibility, Reducing worry and rumination as these drive the individual to gaming behavior, Reducing maladaptive coping responses (particularly cognitive avoidance and procrastination), Teaching more adaptive forms of emotional self-regulation, The presentation will outline the contents of each session and will provide useful outcome measures that can be used to measure effectiveness of treatment with this specific group of patients. The sessions will cover stimulus control and motivation, techniques to reduce impulsivity (by for example long term planning and structure), social skills training, metacognitive techniques, attention training (to strengthen executive control) and emotion regulation techniques. Relapse prevention will be part of the two later sessions. The application of a universal treatment model could lead to multi-site trials across countries therefore making it easier and faster to collect information on what works among this emerging patient group.

GAME AND INTERNET ADDICTION IN THAILAND: CURRENT SITUATION AND COMPREHENSIVE MANAGEMENT

Varoth Chotpitayasunondh (Thailand)

Problems arising from excessive internet use have been documented worldwide including in Thailand where the use of the internet has increased noticeably. Thailand obtained internet access in 1996 as the third country in South East Asia. Since then, the use of the internet has become more popular in the cities and also more accessible to different areas in the country. About 8.6 million people use the internet every day in Thailand and 24 million people have regular access, representing over one-third the population. There are more Facebook users in Bangkok than in any other world city which became the first city in the world with more than 10 million registered Facebook users. Social networking statistics show a very high Facebook penetration in Thailand and the total number of Facebook users in Thailand is reaching 18 million and grew by more than 1.85 million in the last 6 months. Along with the phenomenal growth of the Internet and its use in Thailand, there has been a growing concern nationwide regarding the risks associated with internet over-use and internet addiction. The Internet has a significant potential for providing Thai children and youth with access to educational information, and can be compared with a huge home library. However, the lack of editorial standards and control systems in Thailand limits the Internet’s credibility as a source of information. Recently, game and internet addiction is one of the leading behavioral problems around in Thailand. Prevalence of game addiction
in 4th - 9th grade students reported in 2010 is 13.3%. The other recent study in Thailand found that educational level, marital status of parent, and family relation were found to have significant impact and personality of emotion was the strongest effect factor for internet and game addiction. In conclusion, as a significant number of Thai people these days spend excessive time on the internet, concerns have grown among Thai Government and Mental Health sector over the impact of the Internet on behavior and the possible threats they face in the virtual sphere. Although the government has implemented a number of policies to alleviate addiction, implementing such policies is requiring action; action that is motivated through a better understanding of the risk variables and the negative attributes associated with internet addiction.

COMPARISON OF CLINICAL AND TREATMENT-RELATED FEATURES OF TREATMENT-SEEKING EARLY- AND LATE-ONSET PATHOLOGICAL GAMBLERS
Shin, Y.-C.; Choi, S.-W.; Mok, J.-Y.; Kim, M.-S. (South Korea)

Purposes: This study aimed to examine the differences in the clinical and treatment-related features of pathological gambling (PG) between male early- and late-onset pathological gamblers seeking treatment. Methods: In this study, 381 male outpatients with a primary diagnosis of PG who were treated in a clinical practice were assessed by chart review. We divided the subjects into two groups based on their age of PG onset: early-onset (N=242), with gambling problems at or before age 25, and late-onset (N=139), with gambling problem at or after age 35. Results: The early-onset gamblers were more likely to be a sensation-seeking type (p=0.016) and used significantly more internet-based gambling compared with late-onset gamblers (p<0.001). The preferred type of gambling was strategic gambling in both groups, but the early-onset group was less likely to engage in non-strategic gambling (p=0.016). The early-onset gamblers took anti-craving medication, such as naltrexone (p=0.016) significantly more often and sought treatment significantly more slowly after the onset of PG compared with the late-onset group (12.349.8 years vs. 8.547.5 years for the late-onset group; t=4.24; p<0.001). Although only subjects who stayed in treatment for a minimum of 60 days were included, the mean duration of treatment for the early-onset group was 16.9 months compared with 13.6 months for the late-onset group, although the difference was not statistically significant (p=0.255). Conclusion: The age of onset of PG is associated with several important clinical and treatment features. More studies are needed to investigate and tailor prevention and treatment strategies in each group.

RISK AND PROTECTIVE FACTORS ASSOCIATED WITH PROBLEMATIC SMARTPHONE USE IN UNIVERSITY STUDENTS
Choi, S. W.; Mok, J. Y.; Kim, H. S.; Lee, K. S. and Lee, H. K. (South Korea)

Background and aims: Although smartphone has brought convenience and many entertaining features in daily life, excessive use and danger of addiction should be considered as risky aspects of smartphone. This research aimed to investigate differences of psychological and addiction related feature between normal and problematic smartphone users. In addition, this study also aimed to find out whether characteristic strength and resilience could be functioned as protective factor on smartphone addiction. Methods: A total of 308 university student (male=106, female=191) from three different regions in Korea participated in this research. A questionnaire consisted of Smartphone Addiction Scale, Internet Addiction Test, Beck Depression Inventory, State-Trait Anxiety Inventory-2, Alcohol Use Disorder Identification Test, Fagerstrom Test for Nicotine Dependence, Character Strength Test and Connor-Davidson Resilience Scale was used as a measurement tool. Results: Smartphone addiction high-risk users not only had a greater vulnerability on alcohol and internet addiction than normal users (p<0.01), but also they had a higher anxiety level than normal user group (p<0.05). Furthermore, it was found that self-efficacy-tolerance-recovery (resilience) and temperance (characteristic strength) were influencing protective factors on 5 subtypes of smartphone addiction (p<0.05). Conclusions: People who have high level of self-efficacy, tolerance and power of recovery or people who can control their immediate urges tend to enjoy smartphone use rather than addicted to it. These findings of protective factor on smartphone addiction would contribute to prevent addiction and maintain healthy smart-life.

PREVALENCE AND POPULATION-ATTRIBUTABLE RISK PERCENT OF PATHOLOGICAL GAMBLING IN JAPAN: RESULTS OF A NATIONAL SURVEY OF THE GENERAL ADULT POPULATION

Introduction: A meta-analysis of 119 studies performed in North America found that the lifetime prevalence of pathological gambling is 1.6%. “Pachinko” is the most popular video arcade used for gambling in Japan. The market size is estimated to be 350 billion USD. We conducted a national survey on addictive behavior to
estimate the prevalence of pathological gambling and examined risk factors for this problem. Method: A survey of 7,500 men and women (≥ 20 years) was performed; the sampling was obtained from the total Japanese adult population stratified using a two-stage random sampling in 2008. In addition to the Japanese version of the South Oaks Gambling Screen (SOGS), tests to assess other addictions and the socio-familial background were included in the questionnaire. Replies were obtained from 4,123 people. An SOGS score of five points or more was defined as a pathological gambler. Furthermore, risk factors and the population attributable risk percent (PAR%) of pathological gambling were analyzed. SAS for PC (ver. 9.2) was used for the statistical analyses. Result: The prevalence of pathological gambling was estimated to be 9.04% among men and 1.6% among women. No significant relationships between the rate of pathological gambling and education, marital status, occupation, or income level were seen. The vast majority of male pathological gamblers (93%) used Pachinko as a gambling tool, and about 45% were heavy users who played once a week or more. The odds ratio of Pachinko to pathological gambling was 8.04, and the PAR% was 33.9. Conclusion: This study, the first national survey on pathological gambling, revealed that the prevalence of pathological gambling, especially among men, was much higher in Japan than in other countries. Pachinko, a type of gambling that is unique to Japan, was very popular and was strongly suggested to have contributed to this heightened prevalence.

G. POST-DISASTERS

THE PREVALENCE OF ALCOHOL, NICOTINE, HYPNOTIC ABUSE IN THE EARTHQUAKE AND TSUNAMI STRICKEN AREA IN JAPAN

Mitsuru Kimura, Hiroyuki Sakuma, Sachio Matsushita (Japan)

Introduction: A huge earthquake and following tsunami struck the north-east region of Japan in 2011 and caused serious damage. Mental health problems including substance abuse increased in the area after the disaster. We investigated the prevalence of alcohol, nicotine and hypnotic abuse in the post-disaster area. Subjects and methods: The subjects are 3600 people living in Miyagi and Iwate prefectures where the damage by tsunami was most severe. Interviewers visited the subjects’ home and asked their status of substance use. The subjects underwent self-reporting questionnaires such as alcohol use disorders identification test (AUDIT), Fagerstrom test for nicotine dependence (FTND) and benzodiazepine dependence questionnaire (BDEPQ). 1978 people (54.9%) accepted the interview and 1094 (52.9%) completed the self-report questionnaire. We compared the scores between two groups, the group living in the coastal area with severe damage and the group living in the inland area with relatively minor damage. Results: 4.2% (male) and 11.1% (female) subjects met the DSM-IV criteria for alcohol dependence, 1.2% (male) and 0.2% (female) met the criteria for alcohol abuse. The prevalence of tobacco use and the frequency of subjects whose FTND was more than 7 were significantly higher in the coastal group than in the inland group. The prevalence of hypnotic use and the frequency of the subjects whose BDEPQ score were more than 23 was higher in the coastal group in the female samples, on the other hand, the frequencies of severe alcohol use (more than 6 drinks) was higher in the coastal group in the male samples. The frequency of severe alcohol use was associated with the jobless situation. Conclusion: These results suggest the possibility that alcohol and nicotine related problems are increased in males and hypnotic and nicotine use is increased in females in the disaster-stricken area.

H. COMORBIDITIES

RELATIONSHIPS BETWEEN PTSD, PARTIAL PTSD, EATING DISORDERS AND SUBSTANCE USE DISORDERS IN WOMEN AND MEN IN THE NATIONAL COMORBIDITY SURVEY - REPLICATION STUDY

Brewerton, T. D., Mitchell, K. S. (USA)

Individuals with eating disorders (EDs) characterized by bulimic symptoms have higher rates of substance use disorders (SUDs), and conversely, individuals with SUDs have higher rates of EDs, particularly with bulimic symptoms. Although each group of disorders is reported to have high rates of PTSD or partial/subthreshold PTSD, little is known about the rates of PTSD and partial/subthreshold PTSD in this clinically challenging group.

Using data generated from the National Comorbidity Survey - Replication Study, we tested the hypothesis that...
PTSD and partial or subthreshold PTSD (any PTSD) occur at significantly greater frequencies in individuals who are comorbid for an ED (AN, BN, BED, any binge eating, or any ED) and a SUD (alcohol abuse, alcohol dependence, drug abuse, drug dependence, and a composite variable representing endorsement of “any SUD”). We performed chi-square analyses on these variables (ED x SUD) for women and men separately looking at the rates of SUDs in individuals with neither disorder, an ED only, PTSD or any PTSD only, or both disorders (ED + PTSD/any PTSD). We corrected for the number of analyses done and used alpha = 0.01 as our statistical cutoff for significance. The rates of any SUD were highest in women and men who were comorbid for 1) any ED and PTSD; 2) any ED and any PTSD; 3) any bingeing and PTSD, and; 4) any bingeing and any PTSD. These results suggest that the considerable overlap between EDs and SUDs may be, at least in part, to a history of trauma and the presence of PTSD or significant PTSD symptom. This relationship is especially true for EDs characterized with bulimic symptoms, i.e., binge eating and purging, since the great majority of individuals with EDs identified in the NCS-R had either BN, BED or any bingeing (84% of women, 93% of men).

SUBSTANCE USE SEVERITY AND EATING DISORDER SYMPTOMS IN WOMEN WITH COMORBID PTSD AND SUD


Introduction: Eating disorders (ED) and substance use disorders (SUD) commonly co-occur, especially in conjunction with PTSD, yet little is known about ED symptoms in women presenting to addiction treatment programs. We therefore examined the association between ED symptoms and substance use frequency and severity in a sample of women with comorbid SUD and PTSD enrolled in substance abuse treatment. Method: Participants were 122 women from 4 substance abuse treatment sites who participated in a multi-site clinical trial through NIDA’s Clinical Trial Network (CTN). The Eating Disorder Examination-Questionnaire (EDE-Q) and the Addiction Severity Index (ASI) were administered at baseline. Nonparametric correlation coefficients (Spearman rho) between EDE-Q subscale scores and selected ASI variables were calculated using SPSS. Results: Scores on the Eating Concern, Weight Concern and Shape Concern subscales of the EDE-Q were significantly correlated with past 30 day opiate, cocaine, illicit methadone and polysubstance use, as well as the Addiction Severity Index Drug Subscale score and the number of days experiencing drug problems in the past 30 days. Conclusion: These findings suggest that there may be a relationship between addiction severity and eating disorder symptoms, particularly those involving weight and shape concerns in women with comorbid PTSD and SUD.

INTEGRATING HIV WITH ADDICTION TREATMENT IN COMMUNITY AND CUSTODIAL HEALTHCARE SERVICES

A Kamarulzaman (Malaysia)

People who use drugs are at risk for a number of health related complications including HIV, tuberculosis, viral hepatitis and mental health. Additionally active drug use is associated with difficulties in accessing treatment, adherence and retention. Further adding to the barriers to effective treatment and prevention are health systems issues that often see services for these diseases existing independently resulting in an inefficient system that leads to a myriad of difficulties for the individual patient. Several different models are now emerging to provide more comprehensive and effective services to these patient populations. Co-located integrated care delivery systems or “one-stop shop” should become the focus of national programmes as they continue to scale-up access to antiretroviral medications and treatment of substance abuse for drug users. Existing data suggest that such a programme will expand and improve the effectiveness of prevention and treatment interventions for these individuals. Such integration will require amongst other considerations, cross training of health care practitioners and a change in the health system budgetary and human resource planning.

MARIJUANA AND STIMULANT USE ASSOCIATED WITH INCREASED INCIDENCE OF STI IN PATIENTS RECEIVING TREATMENT AT PUBLIC CLINICS IN US

Haynes, L.F.; Feaster, D.J.; Metsch, L.R. (USA)

Introduction: Understanding the relationship between drug use and risk of sexually transmitted diseases is important for public health policy. Although the use of stimulants has been previously associated with increased risk of STI, marijuana has not been considered a significant risk factor. Objectives: We examine the substance use of individuals presenting for STI testing and the relationship of substance use to the prevalence of STI at baseline. At six month follow-up we examine the relationship between drug use and the incidence of new STI. Methods: 5012 participants were recruited between April and December 2010 among patients seeking treatment at public STI clinics. All participants were tested for chlamydia, gonorrhea, syphilis, HIV and HSV-2; women were
tested for trichomoniasis. Self-reported drug use in the prior 6-months was collected at baseline and six month follow-up. Results: The sample included heterosexual men (38.1%), MSM (27.9%) and women (34%). Most participants, 55.2%, reported using an illegal drug in the prior 6 months; over one-fourth (28.7%) reported drug use other than marijuana and 17.0% reported stimulant use. About a quarter of the sample had DAST-10 scores consistent with severe drug use and 6.1% reported IDU. At baseline, women had higher prevalence of any STI at 55.7% than either males (38.1%) or MSM (37.2%). Amphetamine use was associated with a higher prevalence of STI for MSM at baseline. Crack cocaine use was associated with higher prevalence of STI in all groups. Current IDU was associated with an increased risk for STI across all three subgroups. Stimulant use at baseline was associated with a higher 6-month incidence of STI in women and MSM. Marijuana use at baseline was associated with higher 6-month incidence of STI in women and MSW. Conclusion: Severe drug use is common in this sample of STI clinic patients and is associated with higher prevalence of STI.

I. EDUCATION & TRAINING

INTERNATIONAL EDUCATION AND TRAINING IN ADDICTION MEDICINE

Merrill Herman (USA), Stuart Gitlow (USA), Gabrielle Katrine Welle-Strand (Norway), Mark E Montebello (Australia), Cor de Jong (Netherlands)

Background: In order to have competent doctors to treat patients with Substance Abuse Disorders, the doctors have to receive appropriate education and relevant training. The purpose of this symposium is to give the participants examples of how training is organized in different countries around the world. Outline: The first two presentations will focus on the experience of Addiction Psychiatry Training and Addiction Medicine training in the US. The third presentation will focus on ISAM's newly established network of national contacts in Addiction Medicine Training and give the first results of this autumn's evaluation of how Addiction Medicine Training is performed in approximately twenty countries from all over the world. Australia and New Zealand has had systematic training in Addiction Medicine for many years. The presentation will focus on barriers met in Addiction Medicine Training. The presentation from the Netherlands is about improving conversational skills in Addiction Medicine. The last presentation is from Norway where the government decided in 2012 to establish a full medical specialty in Addiction Medicine. The presentation will focus on the development of this new specialty. The goal is to start the training of new specialists in the autumn of 2014. Conclusion: International cooperation and exchange of experiences in promoting and performing professional Addiction Medicine training can improve the development of Addiction Medicine Education and Training in most countries.

BARRIERS TO ADDICTION MEDICINE TRAINING IN AUSTRALIA AND NEW ZEALAND

Montebello, M. E.; Chen, A.; Hayes, V. (Australia)

Background: The medical workforce is aging, including in the specialty of addiction medicine. If there are to be enough addiction medicine specialists to meet the demands of our growing patient population and community expectations, it is vital that we are able to recruit doctors into specialty training. Method: Previous studies have examined barriers to training in other specialties such as psychiatry. This presentation will examine the significant barriers that exist preventing doctors from entering the addiction medicine training program in Australia and New Zealand. Results: Despite a comprehensive and attractive training program that has existed for more than a decade, the requirement for applicants to first obtain a fellowship in another specialty is turning potential trainees away. This is a requirement that exists in very few other specialties. Discussion: Barriers to training will impact on the development of a specialty medical workforce. Possible solutions to overcoming these barriers will be explored.
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