SAMRC CELEBRATES SCIENCE
E-NEWSLETTER

INFORMATION SERVICES DIVISION
January 2015
SOUTH AFRICAN MEDICAL RESEARCH COUNCIL
TOP 5 ARTICLES

Author: Lu-Anne Swart

Article:

Impact Factor: 4.894

Summary:

Alcohol is involved in a substantial proportion of adolescent homicides in South Africa. To better understand the relationship between alcohol and homicide, the current study sought to describe the blood alcohol concentration (BAC) of adolescent homicide victims in Johannesburg, and to identify the victim and event characteristics associated with a positive BAC at the time of death.

Data on 323 adolescent (15–19 years) homicide victims for the period 2001–9 who had been tested for the presence of alcohol were obtained from the National Injury Mortality Surveillance System (NIMSS). Data included victim demographics, victim BAC levels, weapon or method used, scene, day and time of death.

The study found that alcohol was present in 39.3% of the homicide victims. Of these, 88.2% had a BAC level equivalent to or in excess of the South African limit of 0.05 g/100 ml for intoxication. Multivariate logistic analysis showed that a positive BAC in homicide victims was associated significantly with the victim’s sex [male: odds ratio (OR)=2.127; 95% confidence interval (CI)=1.012–4.471], victim’s age (18–19 years: OR=2.364; CI=1.343–4.163); weapon used (sharp instruments: OR=2.972; CI=1.708–5.171); and time of death (weekend: OR=3.149; CI=1.842–5.383; night-time: OR=2.175; CI=1.243–3.804).

The study shows that excessive alcohol consumption is associated with a substantial proportion of adolescent homicides in Johannesburg, South Africa, and is more prevalent among male and older adolescent victims and in victims killed with sharp instruments over the weekends and during the evenings. Alcohol use is an important target for the prevention of adolescent homicides.
## Figure: Victim and event characteristics by blood alcohol concentration (BAC) in adolescent homicide victims

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
<th>Positive BAC</th>
<th>N (%)</th>
<th>Negative BAC</th>
<th>n (%)</th>
<th>Crude Odds Ratio (^a) (95% CI)</th>
<th>p</th>
<th>Adjusted Odds Ratio (95% CI)</th>
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<td>Male</td>
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<td>18-19 years</td>
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<td>96 (45.9)</td>
<td>113 (54.1)</td>
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<td>2.364 (1.343-4.163)</td>
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<td>20 (50.0)</td>
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<td>Firearm</td>
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<td>Sharp instrument</td>
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<td>45 (45.0)</td>
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<td>Other</td>
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<td>12 (22.6)</td>
<td>41 (77.4)</td>
<td>.394 (.198-.784)</td>
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<td>2.972 (1.708-5.171)</td>
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<td><strong>Scene</strong></td>
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<td>House</td>
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<td>55 (50.0)</td>
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<td>Weekend</td>
<td>193</td>
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<td>95 (49.2)</td>
<td>3.593 (2.179-5.924)</td>
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<td>3.149 (1.842-5.383)</td>
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<td>During the week</td>
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<td><strong>Time</strong></td>
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<td>Night</td>
<td>208</td>
<td>97 (46.6)</td>
<td>111 (53.4)</td>
<td>2.476 (1.506-4.072)</td>
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<td>Day</td>
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<td>.401 (.236-0.682)</td>
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<td>.698 (.258-1.887)</td>
<td>.479</td>
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\(^a\) Crude odds ratios indicate the odds that a victim’s BAC was positive compared to the average of all other categories of that variable.

\(^b\) Other race category includes coloured, white and Indian.

\(^c\) When sharp instrument was replaced with other weapon/method used in the model, all inferences remained the same. For other weapon/method used, OR=0.503 (95% CI=0.237-1.066), \(p=0.073\).

\(^d\) When public place was replaced with house in the model, all inferences remained the same. For house, OR=0.473 (95% CI=0.264-0.848), \(p=0.012\).

\(^e\) When night time was replaced with day time in the model, all inferences remained the same, except that the \(p\) value for victim’s sex increased from .046 to .060 (OR=2.045, 95% CI=0.971-4.306) and public place decreased from .071 to .050 (OR=1.699, 95% CI=1.001-2.884). For day time, OR=0.424 (95% CI=0.233-0.772), \(p=0.005\).
Author: Nkateko Mayevu

Article:


Impact Factor: 4.241

Summary:

Gonadotropin-releasing hormone (GnRH) is the central regulator of reproductive function. It is a decapeptide (pGlu$^1$-His$^2$-Trp$^3$-Ser$^4$-Tyr$^5$-Gly$^6$-Leu$^7$-Arg$^8$-Pro$^9$-Gly$^{10}$-NH$_2$) that binds to receptors in the pituitary. GnRH receptors transduce the GnRH signal across the cell membrane via a change in receptor protein conformation that activates cellular signaling pathways. GnRH analogs have been used to treat a range of reproductive hormone-dependent disorders and the GnRH receptor belongs to the seven-transmembrane G protein-coupled receptor (GPCR) family that includes many important therapeutic drug targets.

Many peptide ligands interact with their receptors via two sites, one that determines binding affinity and a second site that induces receptor activation. Although it is known that the amino-terminal residues of GnRH contribute to receptor activation, the interactions that activate the GnRH receptor are poorly understood. Residues in transmembrane helix seven of GPCRs are important for coupling binding of agonist ligands to changes in conformation that activate the receptors. We hypothesized that the His$^{7.36(305)}$ residue in transmembrane helix seven of the GnRH receptor may contribute to coupling GnRH binding interactions to changes in receptor conformation that activate cytosolic signaling.

Using functional and computational analysis of modified GnRH receptors and peptides, we show that the Trp$^3$ residue of the GnRH peptide is important for full potency in activating the GnRH receptor and that the His$^{7.36(305)}$ residue of the GnRH receptor determines recognition of Trp$^3$ of GnRH. We provide evidence that His$^{7.36(305)}$ of the GnRH receptor forms two distinct interactions that indirectly determine binding of Trp$^3$ and couple Trp$^3$ binding to the receptor activation mechanism that is conserved in GPCRs and initiates cellular signaling.
Figure:

Homology models of the mouse GnRH receptor were built based on the crystal structure of the agonist-bound rNTRI neurotensin receptor. (A) Enlarged view of the wild type GnRH receptor bound to native GnRH showing that Trp3 interacts with Phe7.39(308) and His7.36(305) interacts with carbonyl oxygen atoms of the Val1.30(33) and Ser1.31(34) residues in transmembrane helix 1. The carbon, nitrogen and oxygen atoms of the residues are colored gray, blue, and red, respectively. GnRH is colored cyan. The orientation of transmembrane helices is indicated (TM1 to TM7). The side chains of wild type His7.36(305) (B) or mutant GnRH receptors with Arg7.36(305) (C), Ala7.36(305) (D), Gln7.36(305) (E) are shown in relative to two carbonyl oxygen atoms of the TM1, indicated as 33o and 34o.

Experimental results showed that non-polar His7.36(305) substitutions decreased receptor affinity for GnRH, whereas GnRH signaling potency was more decreased. Uncharged polar His7.36(305) substitutions decreased GnRH potency, but not affinity. [2-Nal]-GnRH retained high affinity at receptors with non-polar His7.36(305) substitutions, supporting a role for His7.36(305) in recognizing Trp3 of GnRH. [2-Nal]-GnRH potency was lower at the wild type GnRH receptor, but unchanged or higher at mutant receptors. Taken together, these results show that a dipole-dipole interaction of the His7.36(305) side chain is required for high affinity binding of GnRH, whereas an additional ion-dipole interaction of His7.36(305), which can be mimicked by Arg, but not other substitutions, is required for full activation of the receptor by GnRH. This suggests that the ion-dipole interaction couples the ligand binding pocket to the conserved GPCR activation mechanism.
Author: Nathlee Abbai

Article:

Impact Factors: 4.232

Summary:

Point of care tests for gonorrhoea can be beneficial and cost effective in high prevalence populations. We evaluated a rapid point of care test, the OneStep Gonorrhea RapiCardTM InstaTest for the detection of Neisseria gonorrhoeae in specimens collected from men and women attending a public health clinic in KwaZulu-Natal. The diagnostic performance of the test was compared to culture and the BDProbeTecET PCR Assay. The overall prevalence of N. gonorrhoeae, diagnosed using PCR and culture was 31.3% (23.9-39.8) and 27.5% (20.4-35.8) respectively. The calculated test performance for the rapid test when compared to PCR was as follows: sensitivity 34.1% (20.9-50.4), specificity 97.8% (91.3-99.4), positive predictive value 87.5% (57.0-97.4) and negative predictive value 76.5% (67.8-83.4). When compared to culture, the rapid performed as follows: sensitivity 33.3% (19.4-50.9), specificity 95.8% (89.1-98.4), positive predictive value 75% (45.7 - 91.4) and negative predictive value 79.1% (70.6-85.7). By gender, the prevalence of N. gonorrhoeae reported with PCR was significantly higher in males when compared to females, 54.9% (41.0-68.1) and 16.25% (9.6 – 26.2) respectively, p-value <0.001. Similar observations was reported for culture, prevalence of N. gonorrhoeae was 52.9% (39.1-66.3) in males and 11.25 % (5.9-20.4) in females. Additionally, the OneStep Gonorrhea RapiCardTM InstaTest showed a higher diagnostic accuracy for male patients when compared to female patients. The findings in this study emphasize the need for more sensitive rapid tests for N. gonorrhoeae to be developed taking into account sample type, site of sampling and microbial load needed for detection.
TABLE 1 Overall diagnostic performance of the OneStep GenoType RapiCard InstaTest compared to the BDProbeTec ET SDA assay and culture

<table>
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<tr>
<th>Assay/culture diagnostic results</th>
<th>Positive (n)</th>
<th>Negative (n)</th>
<th>Total (n)</th>
<th>Sensitivity (% [95% CI])</th>
<th>Specificity (% [95% CI])</th>
<th>PPV (% [95% CI])</th>
<th>NPV (% [95% CI])</th>
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<tr>
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<td>42</td>
<td>33.3 (20.4–46.6)</td>
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<td>75 (45.7–91.4)</td>
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*CI, confidence interval.
*bOne-sided, 97.5% CI.
Author: Zhuo Fang

Article:
DOI: 10.1016/j.tube.2015.01.004
Impact Factor: 3.503

Summary:
Iron is an essential element to most life forms including mycobacterial species. However, in the oxidative atmosphere iron exists as insoluble salts. Free and soluble iron ions are scarce in both the extracellular and intracellular environment which makes iron assimilation very challenging to mycobacteria. Tuberculosis, caused by the pathogen, Mycobacterium tuberculosis, is one of the most infectious and deadly diseases in the world. Extensive studies regarding iron acquisition strategies have been documented in mycobacteria, including work on the mycobacterial iron chelators, the iron-responsive regulon, and iron transport and utilization pathways. Under low iron conditions, expression of the genes encoding iron importers, exporters and siderophore biosynthetic enzymes is up-regulated significantly increasing the ability of the bacteria to acquire limited host iron. Disabling these proteins impairs the growth of mycobacteria under low iron conditions both in vitro and in vivo, and that of pathogenic mycobacteria in animal models. Drugs targeting siderophore-mediated iron transport could offer promising therapeutic options. However, the discovery and characterization of an alternative iron acquisition mechanism, the heme transport and utilization pathway, questions the effectiveness of the siderophore-centered therapeutic strategy. Links have been found between these two distinct iron acquisition mechanisms, thus, targeting a few candidate proteins or mechanisms may influence both pathways, leading to effective elimination of the bacteria in the host.
Figure:
Author: Georgia Schäfer

Article:

Impact Factor: 3.368

Summary:
The fibrillar collagen scaffold of the extracellular matrix provides a structural framework for cells in tissues and regulates intercellular communication; its disregulation has been associated with tumour development and progression. Previous work has shown that expression of type I collagen, the most abundant mammalian extracellular matrix protein, is decreased in chemically or virally transformed cells. This negative regulation could be mapped to a proximal COL1A2 promoter element spanning a CME (Collagen Modulating Element) site in SV40-transformed human fibroblasts (SV-WI38) that binds an unknown repressing protein. By magnetic bead pull-down, we observed a multiprotein complex bound to the CME with preference for single-stranded over conventional double-stranded DNA. MALDI-TOF mass spectrometry of the CME-binding protein complex revealed involvement of nuclear annexin A2 (AnxA2) which was increased in SV40-transformed cells. Further EMSA analysis demonstrated that AnxA2 did not directly bind to the DNA but stabilised the complex and led to an increase in protein binding to the CME in SV-WI38 but not untransformed WI38 cells. Knockdown of AnxA2 by siRNA increased type I collagen production in both WI38 and SV-WI38 cells; however, these effects were not mediated at the transcriptional level. Rather, our data indicate a novel functional role of AnxA2 in the negative post-transcriptional regulation of type I collagen synthesis in human fibroblasts. In SV40-transformed cells, AnxA2 is accumulated at the proximal COL1A2 promoter region, suggesting close association with the transcriptional machinery that possibly facilitates binding to the emerging mRNA, eventually contributing to overall repression of type I collagen protein synthesis.
PUBLICATIONS

1. **INTRAMURAL RESEARCH UNITS**

   Alcohol, Tobacco and Other Drug

      DOI:10.7196/SAMJ.9260
      **Impact Factor:** 1.712

      DOI: 10.1007/s10899-015-9522-5
      **Impact Factor:** 1.753

      DOI: 10.15805/addicta.2014.1.2.023
      **Impact Factor:** None

   Biostatistics

      DOI:10.7196/SAMJ.8369
      **Impact Factor:** 1.712

   Centre for Tuberculosis

      DOI: 10.1097/QAD.0000000000000536
      **Impact Factor:** 6.557

      DOI: 10.1016/j.tube.2015.01.004
      **Impact Factor:** 3.503

      DOI: 10.1111/tbed.12329
      **Impact Factor:** 3.116
Impact Factor: 29.648

Impact Factor: 1.208

Impact Factor: 11.986

Environment and Health
Impact Factor: 1.485

Health Systems
Impact Factor: 2.194

Non-Communicable Disease
Impact Factor: 0.373

Impact Factor: 2.296
Impact Factor: 2.536

Diabetes Discovery Platform
DOI: 10.3390/nu7020815
Impact Factor: 3.148

South African Cochrane Centre
DOI:10.7196/samj.8819
Impact Factor: 1.712

DOI: 10.1002/14651858.CD006495.pub3
Impact Factor: 5.939

Violence, Injury and Peace
DOI: 10.1111/add.12825
Impact Factor: 4.894

2. SAMRC RESEARCH OFFICES
Cancer
Impact Factor: 1.712

3. EXTRAMURAL RESEARCH UNITS
Anxiety and Stress Disorders
DOI: 10.1007/s12325-015-0176-6
Impact Factor: 2.438
   **Impact Factor: 5.939**

   **Impact Factor: 3.323**

**Bioinformatics Capacity Development**

   **Impact Factor: 4.829**

**Developmental Pathways for Health**

   **Impact Factor: 1.646**

   **Impact Factor: 2.950**

**Drug Discovery and Development**

   **Impact Factor: 4.097**

**Exercise and Sports Medicine**

   **Impact Factor: 7.000**
   **Impact Factor: 1.490**

**Health Policy**

1. **Rispel LC, Cloete A, Metcalf CA.** 'We keep her status to ourselves': Experiences of stigma and discrimination among HIV-discordant couples in South Africa, Tanzania and Ukraine. SAHARA Journal. 2015 Jan 1. DOI: 10.1080/17290376.2015.1014403
   **Impact Factor: 0.393**

**HIV Prevention**

   **Impact Factors: 4.232**

**Inter-University Cape Heart**

   DOI: 10.2144/000114246
   **Impact Factor: 2.754**

**Medical Imaging**

   DOI: 10.1007/s00247-014-3255-γ
   **Impact Factor: 1.651**

**Receptor Biology**

   DOI: 10.1016/j.mce.2015.01.008
   **Impact Factor: 4.241**

   DOI: 10.1074/jbc.M114.612606
   **Impact Factor: 4.600**
DOI: 10.7196/SAMJ.8185  
**Impact Factor: 1.712**

DOI: 10.1002/jcb.24989  
**Impact Factor: 3.368**

**Respiratory and Meningeal Pathogens**

DOI: 10.1186/s12879-015-0746-x  
**Impact Factor: 2.561**

**Rural Public Health and Health Transition**

DOI: 10.3402/gha.v8.25912  
**Impact Factor: 1.646**

4. **GRANT FUNDED RESEARCH**

**Self-Initiated**

Grants and Scholarships Administration

DOI: 10.1016/j.socscimed.2015.01.046  
**Impact Factors: 2.558**

DOI:10.7196/samj.8394  
**Impact Factors: 1.712**

DOI: 10.1111/bcp.12590  
**Impact Factor: 3.688**
**Impact Factor: 3.489**

**Research Admin and Management**

**Impact Factor: 1.966**

**Impact Factor: 2.507**

**Impact Factor: 4.085**

**Strategic Research Initiatives**

1. **Atashi F**, Modarressi A, **Pepper MS**. The Role of Reactive Oxygen Species in Mesenchymal Stem Cell Adipogenic and Osteogenic Differentiation: A Review. Stem Cells and Development. 2015 Jan 20. DOI: 10.1089/scd.2014.0484
**Impact Factor: 4.202**

2. Mellet J, Alessandrini M, Steel HC, **Pepper MS**. Constituting a public umbilical cord blood bank in South Africa. Bone Marrow Transplant. 2015 Jan 26. DOI: 10.1038/bmt.2014.329
**Impact Factor: 3.466**

**SHIP**

**Impact Factor: 9.808**

**Impact Factor: 2.581**
South African AIDS Vaccine Initiative


Impact Factor: 2.194

5. CLOSED RESEARCH UNITS

Clinical and Biomedical Tuberculosis


Impact Factor: None

6. RESEARCH UNITS WITH NO QUALIFYING PUBLICATIONS

INTRAMURAL

- Burden of Disease
- Gender and Health

SAMRC RESEARCH OFFICES

- AIDS
- Malaria
- Tuberculosis

EXTRAMURAL

- Cancer Epidemiology
- Diarrhoeal Pathogens
- Human Genetics
- Immunology of Infectious Disease
- Maternal and Infant Health Care Strategies
- Molecular Mycobacteriology
## 7. GRANTS AWARDED

### LIST OF NEW CONTRACTS – 31 JANUARY 2015

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<tr>
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<th>Main Funder</th>
<th>Project Title/Description</th>
<th>Contract Value</th>
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<td>Wellspring Advisors, LLC</td>
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<td>National Institute of Allergy Infectious Disease</td>
<td>Leadership and Operations Centre (LOC): Microbicide Trial Network</td>
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<td>Department of Science and Technology</td>
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