

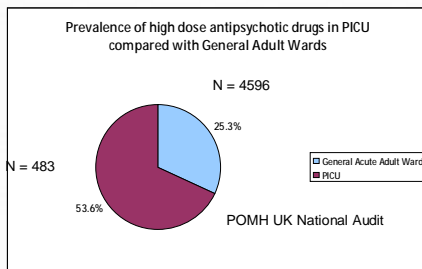
## The Clinical and Diagnostic Utility of Creatine Kinase in the Diagnosis of Neuroleptic Malignant Syndrome (NMS)

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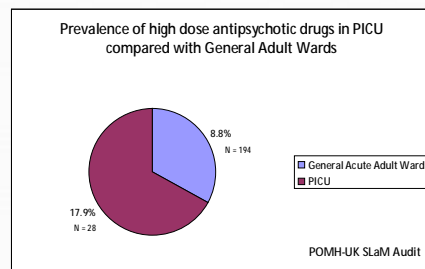
## Increased risk in PICU

- Clinical risk is high in Psychiatric Intensive Care
- Violence/aggression
- Rapid tranquilisation
- Inadequate physical health monitoring
- Antipsychotic high dose and combination treatments more prevalent

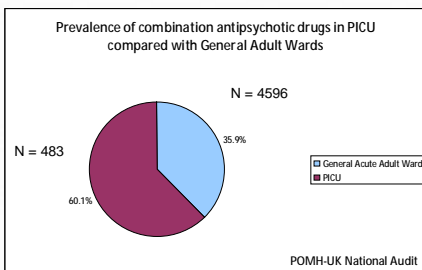
### High dose antipsychotic prescribing on PICU - National



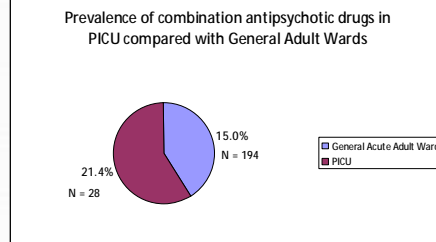
### High dose antipsychotic prescribing in PICU - SLAM



### Prevalence of antipsychotic combination on PICU - National



### Prevalence of antipsychotic combination on PICU - SLAM



## Risk factors for NMS

### Risk factors in neuroleptic malignant syndrome. A case-control study

Veiga LP, Marder S, Patel P, Finn JL, Sanchez RA. *Cell Tissue Res Neuroleptic Malignant Syndrome: A Case-control Study*. *Acta Psychiatrica Scand* 2003; 107: 42-49. © Blackwell Munksgaard 2003.

**Objective:** To determine whether environmental temperature, agitation, serotonergic use, onset of extrapyramidal, and a history of chronic disease were risk factors for neuroleptic malignant syndrome (NMS).

**Method:** Cases and age- and sex-matched psychiatric controls admitted to a regional acute psychiatric unit over a 10-year period.

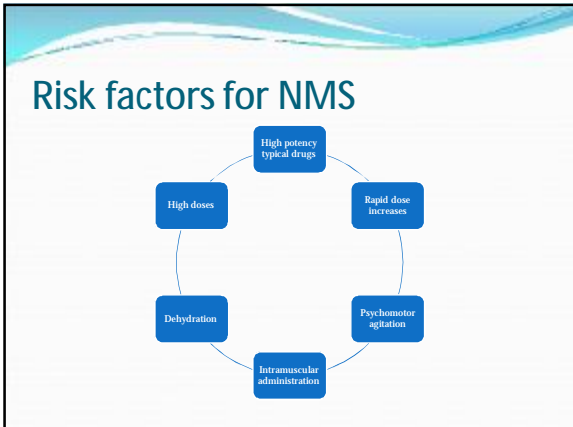
**Results:** Both age- and environment-related variables by logistic differences between patients with NMS ( $n = 11$ ) and controls ( $n = 41$ ) with regard to the presence of onset of extrapyramidal, psychomotor agitation, and a number of variables relating to intramuscular administration, and domain. We found no differences between NMS patients and psychiatric controls in respect of changes in environmental temperature.

**Conclusions:** Our study supports the need for caution when using intramuscular administration, already increasing, high-dose neuroleptics, particularly in non-air conditioned or agitated patients, regardless of environmental temperature.

**Keywords:** neuroleptic malignant syndrome, extrapyramidal symptoms, rapid medication, intramuscular medication, high-dose neuroleptics, agitation.

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## Antipsychotic monitoring recommendations

	On initiation	Continued treatment
All antipsychotics	Weight	3-6 monthly
	Blood glucose	Annually
	Blood pressure	3-6 monthly
	Cholesterol	Annually
	Blood urea	Annually
	Prothrombin time	Annually
	ECG	Annually
	Full blood count	Annually
	Liver function	Annually
	Renal function	Annually
ECG	Annually	

## Baseline monitoring of Creatine Kinase

- Baseline CK measurements done infrequently
- First episode psychosis
- N = 64
- Monitoring of baseline CK in 14 (22%)
- Range: 57 – 5668 IU/L
- 6/14 patients with CK > 150 IU/L

## What is NMS?

- Neuroleptic malignant syndrome (NMS) is an idiosyncratic, life-threatening reaction to antipsychotic medication, characterized principally by delirium, fever, autonomic instability, and muscular rigidity

But

- There is no universally agreed criteria for NMS

- ## DSM IV Diagnostic Criteria
- Essential symptoms
    - Severe muscle rigidity
    - Elevated temperature >37.2°C associated with use of antipsychotics
  - Associated symptoms
    - Impaired consciousness
    - Mutism
    - Tremor
    - Dysphagia
    - Diaphoresis
    - Elevated or fluctuant BP
    - Raised CK
    - Raised WCC
    - Incontinence

## Diagnostic criteria for NMS

- Levenson
- Addonizio et al
- Pope et al
- Adityanjee et al
- Friedman et al
- Caroff et al

## - Raised CK does not equate to NMS

### Ascertaining instances of neuroleptic malignant syndrome in a secondary mental healthcare electronic medical records database: the SLAM BRC Case Register

Chin-Kuo Chang, Simon Harrison, William Lee, David Taylor and Robert Stewart

#### Abstract:

**Objective:** Neuroleptic malignant syndrome (NMS) is a rare but potentially fatal complication of antipsychotic treatment. However, there is no single diagnostic test and a variety of overlapping criteria exist. Using a large case register of secondary mental healthcare in Southeast London, we aimed to identify suspected cases and quantify the levels of agreement between six different diagnostic criteria previously published.

**Methods:** Taking advantage of a recently developed case register sourced from full but unorganized electronic medical records (the South London and Maudsley NRG Foundation Trust), we applied text string searching to identify suspected NMS cases for which action had been taken to investigate or treat. Three psychiatrists manually reviewed case records for clinical data to compare diagnostic criteria.

**Results:** Analysis of the case register revealed 183 suspected NMS cases, of which 43 fulfilled at least one set of the six diagnostic criteria. Agreement between criteria was poor ( $\kappa = 0.25$  for all combined agreement, 95% confidence interval 0.21–0.29) and only one case fulfilled all six diagnostic criteria. However, among cases meeting any diagnostic criteria, pyrexia, autonomic symptoms, altered consciousness, autonomic symptoms, and elevated CK concentrations were significantly more common than in cases not meeting diagnostic criteria ( $p < 0.01$ ). On further analysis, the presence of two or more of these features significantly distinguished cases meeting criteria from those that did not ( $p < 0.01$ ). Individual symptoms were also reported in suspected cases of NMS that did not fulfil any diagnostic criteria.

## Diagnosis of NMS

Table 2. Number of cases meeting number of sets of criteria (N = 183)\*

Number of sets met	Number of cases (%)	Cumulative number of cases (%)
6	1 (0.55)	1 (0.55)
5	3 (1.64)	4 (2.19)
4	5 (2.73)	9 (4.92)
3	5 (2.73)	14 (7.65)
2	32 (17.5)	46 (25.1)
1	137 (74.7)	183 (100)
0	140 (76.5)	183 (100)

\*For Pope's criteria, probable cases were considered as non-neuroleptic malignant syndrome.

## Causes of raised CK

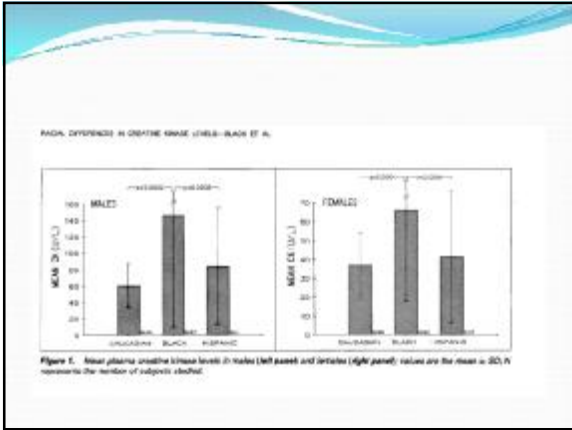
- Cardiac causes
  - Cardioversion
  - Myocarditis
  - Pulmonary edema
- Skeletal muscle disease
  - Dermatomyositis
  - Muscular dystrophy
  - Myasthenia gravis
  - Rhabdomyolysis
- Metabolic disease & drugs
  - Alcoholism
  - Diabetes mellitus
  - Malignant hyperthermia
  - Hypothyroidism
  - Statins
- CNS disease
  - Acute brain injury
  - CVA
  - Seizures

## Racial differences in CK levels

### Racial Differences in Serum Creatine Kinase Levels

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Total creatine kinase was measured in serum samples obtained from 207 asymptomatic healthy subjects, 112 men and 95 women, during screening visits to the Yale University Hypertension Clinic or the Yale-New Haven Hospital Primary Care Center or during pre-enrollment clinical examinations of the Yale-New Haven Hospital Primary Care Clinic. The group consisted of 147 whites, 132 blacks, and 28 Hispanics. Blood pressure was measured in all patients, and weight, height, and serum potassium and creatinine levels were determined in most. Any subject who had engaged in any vigorous exercise in the 12 hours prior to the visit was excluded. The mean total creatine kinase level for blacks was 148.5  $\pm$  106.0 units/liter (median, 100 units/liter), the mean level for whites was 60.0  $\pm$  38.1 units/liter (median, 31 units/liter), and the mean level for Hispanics was 64.0  $\pm$  73.8 units/liter (median, 47 units/liter). The mean total creatine kinase level was 4.4  $\pm$  3.0 times greater (median, 1.6 times greater), the mean



## Racial differences in CK levels

—“In summary, our results clearly show that black men and black women have a higher mean total creatine kinase level than whites or Hispanics and that the majority would be considered to have abnormal levels if the usual laboratory values are used”

— Black et al, Am J Med, 1986

### Creatine Kinase Activity Is Associated With Blood Pressure

Larry M. Berwick, MD, Gilbert Martinez, MD, Haris R. Wachtman, MD, Richard P. Knappus, MD, PhD, Joseph F. Clark, PhD, Gust A. van Marrewijk, MD, PhD

**Background**—We previously hypothesized that high activity of creatine kinase, the central regulatory enzyme of energy metabolism, facilitates the development of high blood pressure. Creatine kinase rapidly provides adenosine triphosphate to highly energy-demanding processes, including cardiovascular contraction, and adenosine triphosphate enables neuronal function. Relatively high activity of the enzyme, particularly in resistance arteries, is thought to enhance pressure-regulated myosin blood pressure. Thus creatine kinase activity is expected to be high in black people, a population subgroup with greater hypertension risk, the proposed effects of high creatine kinase activity, however, are not “race-dependent.” We therefore assessed whether creatine kinase is associated with blood pressure in a multiracial population.

**Methods and Results**—We analyzed a stratified random sample of the population of Amsterdam, the Netherlands, consisting of 1444 subjects (50% white European, 32% South Asian, 18% black, and 10% of other ethnicity) aged 56 years. We used linear regression analysis to investigate the association between blood pressure and natural serum creatine kinase after controlling for a multitude of covariates of blood pressure. Creatine kinase was independently associated with blood pressure, with an increase in systolic and diastolic pressure, respectively, of 0.21 (95% CI, 0.1 to 0.3) and 0.13 (95% CI, 0.0 to 0.2) mm Hg per log creatine kinase increase after adjustment for age, sex, body mass index, and ethnicity.

**Conclusions**—Creatine kinase is associated with blood pressure. Further studies are needed to explore the nature of this association, including how variation in endogenous creatine kinase activity may affect pressure response. *Circulation*. 2006;114:2056-2060.

Key Words: creatine kinase • blood pressure • metabolism • muscle, smooth • white race

### Increased CK is not uncommon in febrile illness

#### Significance of Elevated Levels of Serum Creatine Phosphokinase in Febrile Disease: A Prospective Study

David Cohen, Leonard Faberick, Dale Strydom, and Arthur J. Waisbich

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### Effect of intramuscular injection on CK levels

Effect of Intramuscular Injections on Serum Creatine Phosphokinase Activity

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S. Mizak  
and  
M. Boyer

(From the Department of Psychiatry, University of Illinois Chicago, Illinois)

### Exercise and raised CK

#### Creatine kinase monitoring in sport medicine

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Aims of general agreement: Total creatine kinase (CK) levels depend on age, gender, race, muscle mass, physical activity and chronic conditions. High levels of serum CK in apparently healthy subjects may be associated with physical training status, as they depend on numerous damage stimulus sources that damage skeletal muscle cells results in increased total serum CK. The highest concentrations serum enzyme activities are found after prolonged exercise such as ultramarathon running or weight-lifting exercises and downhill running, which include eccentric muscle contractions. Total serum CK activity is markedly elevated for 2-6 days after the exercise bout and, when patients end, it gradually returns to basal levels. Pathologically increased serum CK levels are increasingly associated in healthy individuals and are also markedly increased in the preclinical stages of muscle diseases.

