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Request of collaboration to recruit experts for the EFLM Task & Finish Group " Biological markers of diagnosis and follow-up of nitrous oxide abuse. "

Dear Colleagues,
I am delighted to present you the new EFLM Task & Finish Group entitled « **Biological markers of diagnosis and follow-up of nitrous oxide abuse** » which I have been asked to Chair.

Aims of project

Recreational use of nitrous oxide (N2O) has increased exponentially recently and leads to neurological disorders including subacute combined degeneration of spinal cord. A recent report from European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) showed that the recreational use of N2O is a growing and major concern in Europe.
For biological monitoring, serum or urine N2O assays are not routinely performed because they do not allow to ensure a real exposure due to the very short half-life of this gas in the body. Literature links the clinical symptomatology of N2O intoxication to vitamin B12 inactivation. However, isolated serum vitamin B12 assay does not seem to be a suitable marker for assessing N2O intoxication because it is neither sensitive nor specific. Functional disorders of vitamin B12 metabolism, characteristic of N2O intoxication, could be explored by two plasma markers: homocysteine and methylmalonic acid (MMA). Indeed, Vitamin B12 is the cofactor of two enzymes: methionine synthase using methylcobalamin and methyl-malonyl-CoA mutase (MMA-CoA-mutase) using adenosylcobalamin. Oxidation of cobalamin by N2O decrease formation of methylcobalamin from cobalamin, leading to decrease of methionine synthase activity, which cannot transform homocysteine into methionine (component of myelin). A similar effect on MMA-CoA-mutase another vitamin B12 dependent enzyme was also suspected, which transform methylmalonic acid (MMA) into succinyl-CoA but still debate. Literature report inconstant MMA increase in case of N2O consumption. However, alteration of vitamin B12 metabolism cannot explain all pathophysiological processes and remain still poorly understood.
Therefore, there are currently no biological recommendations for the diagnosis and follow-up of nitrous oxide abusing patients. It is therefore necessary to bring together a group of experts (both clinical chemist and clinicians such as neurologist and emergency department) in order to determine the appropriate biological parameters for the follow-up and monitoring of patients with associated clinical complications.

Proposed plan of action for the first two years

1. State of the art and assessment of current needs.
    a) Each country practices for diagnosis and follow-up, epidemiology
    b) Current publications and literature recommendations
    c) Write a review of the literature (intended journal: CCLM)
    d) Determination of clinical trial needs
2. Implementation and/or evaluation of existing clinical trials (6- XX months)
    a) To make the state of the clinical trials currently in progress (for example in France, we have currently in progress a clinical trial on the subject BALON NCT: 05540561)
    b) To follow the progress of these clinical trials and the expected benefits for the recommendations
    c) To provide a European force on results sharing and international cooperation for these ongoing clinical trials.
    d) Monitor academic calls for projects or possible industrial partnerships and provide advice for the writing of these calls for projects.

Based on clinical trials and literature data, selection of biomarkers of interest and recommendation writing (6-XX months): will depend on the existence or not of ongoing clinical trials

Terms of references for the project

1- To promote relation between biologists and clinicians (neurologists and emergency physicians) for manage patient with nitrous oxide abuse
2- To provide recommendations on biological markers to be used in the diagnosis and follow-up of the nitrous oxide abusing patient.
3- To provide a scientific paper and a feedback report summarizing the main findings of literature and clinical trial associated.

Applications

Experience of working with biological markers related to nitrous oxide (**especially nutrition and metabolism**) and Laboratory Medicine at local or national level is required.

Please provide a short resume that provide experiences in the field.

Applications should be submitted directly to the chair Office to the attention of guillaume.grzych@chu-lille.fr and protoxyde@chu-lille.fr.

Dr Grzych Guillaume