Which is the best way of using nitrous oxide for treatment and research in neuropsychiatry?

I welcome the excellent paper by Guimaraes et al. which extends research on nitrous oxide (N₂O) in neuropsychiatry—a neglected field, since our initial work in 1982 and then 1985 indicating that low, anxiolytic, and non-anaesthetic doses of N₂O ameliorate depression. Research has demonstrated that N₂O, at subanaesthetic concentrations acts on opioid receptors. We therefore concluded that the antidepressant activity of N₂O occurred via opioid activity.

Interestingly, this latest work confirms our findings that the antidepressant action of N₂O occurred immediately and endured after gas administration. It also supports our unpublished observation that the gas could be used as an adjuvant to routine antidepressant medication.

Like Nagele’s group, Guimaraes et al. believe that N₂O and ketamine are antidepressant mainly via antagonism of the N-methyl-D-aspartate receptor (NMDAr). However, they provide two key references disputing NMDAr involvement. One showed that naloxone blocks the antidepressant action of ketamine, and the other that NMDAr antagonists (like memantine) are not antidepressant. These references and our work indicate that opioid receptors are more likely to be responsible for the antidepressant action of N₂O and ketamine. Indeed, NMDAr blockade occurs only at N₂O concentrations which are anaesthetic and not subanaesthetic, making it unlikely that the NMDAr mediates the antidepressant action observed.

The dental technique (using identical equipment as here) never has a fixed goal-concentration, but titrates N₂O using each individual’s dose-response to reach concentrations achieving maximum relaxation while maintaining consciousness. In short, the concentration varies, depending on each individual’s dose-response to N₂O. Apart from avoiding anaesthesia it also minimises side effects.

Because a relatively loose nasal mask was used without N₂O end tidal measurements the inhaled gas concentration at the alveolus cannot be assumed. Thus, the reading of 50% on the rotameter alone is a poor reflection of the actual gas volume inhaled. Indeed, nasal masks produce N₂O concentrations at the alveolus which are less than half the rotameter setting.

Guimaraes et al chose 50% N₂O mistakenly believing that it produces minimal sedation and refer to the American Anesthesiology Association Guidelines. These guidelines clearly states: “less than 50%” N₂O is required to produce minimal sedation, which encompasses the dental titration method. Since a fixed goal concentration ignores the individual sensitivities to the gas, it is unsurprising that they “could find no data” giving the “best concentration of N₂O” for depression. Perhaps, this indicates that the correct antidepressant dose is best achieved by titrating, to each individual’s requirements, without an anaesthetist.

Disclosure

MAG has been researching the psychotropic properties of nitrous oxide for over 40 years. Since 2003 he has been a medical adviser to Sedatek, a South African company that supplies equipment for nitrous oxide in South Africa, predominantly among dentists; he owns no shares in the company.

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References