



Mini-Review: A Brief History of Nitrous Oxide (N₂O) Use in Neuropsychiatry



Mark A. Gillman*

South African Brain Research Institute, 6 Campbell St. Waverley 2090, Johannesburg, South Africa

Abstract: Background: Joseph Priestley's discovery of nitrous oxide (N₂O) was recorded in 1772. In the late 1790's, Humphry Davy experimented with the psychotropic properties of N₂O, describing his observations in a book, published in 1800. A dentist, Horace Wells discovered anaesthesia with N₂O in 1844. Over a century after Davy, its potential usefulness in psychiatry was first recognised. The seminal researches in neuropsychiatry, between 1920 and 1950, mainly used anaesthetic concentrations of the gas. The psychotropic actions of N₂O, at non-anaesthetic doses, were first used by dentists, mainly for its anxiolytic action. In modern dentistry, N₂O is always mixed with at least 30% oxygen and titrated to doses rarely exceeding 40% of N₂O. At these lower concentrations, untoward effects are almost always avoided, including over-sedation and/or anaesthesia. In the early 1980's, the low-dose dental titration technique was first used to investigate and treat psychiatric conditions, including substance abuse. Until then, most physicians regarded the gas only as an anaesthetic agent. An exception was obstetricians who used a fixed 50% concentration of N₂O diluted with oxygen for analgesia during parturition. In 1994, to clearly distinguish between anaesthetic and non-anaesthetic concentrations (as used in dentistry), the term Psychotropic Analgesic Nitrous oxide (PAN) was introduced.

Objective: This paper will give a brief history of the use of the N₂O in psychiatry since the psychotropic actions were first recognised in the 18th century until the present.

Conclusion: The role of other non-opioid systems, and the extent to which they contribute to the psychotropic properties of N₂O, still remains to be established.

Keywords: Psychotropic analgesic nitrous oxide, N₂O, dental titration, neuropsychiatry, substance abuse, psychiatry, neurology.

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1. INTRODUCTION

Nitrous oxide (N₂O) and its psychotropic properties have been known to man for more than two centuries [1, 2]. The pioneers investigated its psychotropic properties with either pure N₂O or a mixture of the gas with oxygen [2]. It was only much later, *i.e.* in the 20th Century that the potential of the gas to investigate and treat psychiatric conditions occurred, predominantly at anaesthetic concentrations. Not until the early 1980's was it first used in neuropsychiatry at much safer, lower concentrations, where anaesthesia is avoided. Here, it was titrated so doses seldom exceeding 40% N₂O with accompanying concentration of oxygen of 60% or more. Apart from administering a personalised dose for each patient, this titration technique much reduces or almost totally avoids side effects [1, 3, 4]. The most recent research features a fixed 50% mixture of N₂O with oxygen applied via a full-face mask [5]. Unfortunately, doses of 50% tend to produce more unpleasant side-effects, since the amounts of N₂O are not tailored to the needs of each subject [1, 3, 4, 6] and are also usually above the requirements of most subjects [3, 4]. Table 1 highlights the main milestones in history of the use of N₂O in neuropsychiatry since the 18th Century.

2. RESEARCH IN THE 18th AND 19th CENTURIES

Joseph Priestley synthesised nitrous oxide (N₂O) and reported on his findings in 1772 [2]. In the last few years of the 18th Century, Humphry Davy investigated the chemistry of the gas as well as its psychotropic properties. In 1800, he published the observations on the gas in his classical book 'Researches, chemical and philosophical; chiefly concerning nitrous oxide: or dephlogisticated nitrous air, and its respiration' [7]. He breathed both 100% N₂O and mixtures of the gas diluted with oxygen or air. He also introduced the gas to a number of friends and associates, including the poets Coleridge and Southey [7].

At that time, practically nothing was known about the dangers of N₂O, except that if air was excluded and the pure gas breathed, warm-blooded animals died within minutes. Davy was clearly an extremely brave, if a foolhardy young man, whose scientific curiosity outweighed any potential dangers of asphyxiation or other, as yet unknown, toxic effects of the gas. Apart from describing its analgesic actions, he was also the first to mention its psychotropic properties; including anxiolysis and euphoria. In addition, he also noted how the gas ameliorated an alcoholic withdrawal state that he himself had experienced [7]. An observation only further researched, almost 2 centuries later [1]. Davy's book [7] is teeming with other insightful and accurate observations that attest to his perspicacity and brilliance as a scientist.

*Address correspondence to this author at the Emeritus CEO: South African Brain Research Institute, 6 Campbell St Waverley 2090, Johannesburg, South Africa; Tel: +27117862912, E-mail: mag@iafrica.com

Table 1. Main milestones in the history of the use of nitrous oxide in neuropsychiatry.

Date	Concentration and Method	Event & Investigator/s
1772		Priestley discovers and synthesises N ₂ O [2]
1800	Non-titrated/concentration unknown	Davy's first monograph published detailing research of its psychotropic properties (euphoria, analgesia, acute alcohol withdrawal) and other properties [7]
1844	Anaesthetic	Wells discovers Anaesthesia – first surgical procedure [2, 8, 9]
1881	Non-anaesthetic consistent with PAN	Klikovich - MD Thesis awarded on use of anxiolytic properties of PAN in medicine & obstetrics and various medical conditions (asthma and coronary heart disease) [10]
1928	Anaesthetic	Zador studies use of N ₂ O in neuropsychiatry (depression, schizophrenia, movement disorders) [9]
1944	Anaesthetic	Rogerson investigates N ₂ O for psychotherapy [17]
1968	PAN	Langa initiates large-scale use N ₂ O as an anxiolytic in dentistry [26]
1970	Fixed -50% N ₂ O:50%O ₂ *	MacDonald uses N ₂ O for psychoanalysis [31]
1972	Fixed-50% N ₂ O:50%O ₂ *	Kripke & Hechtman uses N ₂ O (analgesia & opioid withdrawal) [32]
1976	median dose-55%*	Berkowitz <i>et al.</i> provide animal evidence that N ₂ O interacts with EOS [32]
1980-1983	PAN	Gillman <i>et al.</i> use N ₂ O to: demonstrate direct and indirect actions of the gas with EOS in man [14, 19, 51, 52]; uncover the biological principle of gaseous neurotransmission [14, 19, 23, 24]; provide evidence that human sexual response is mediated by EOS [54]; uncover first biological link (EOS) on pain-pleasure continuum [51, 52, 54].
1982	PAN	Lichtigfeld & Gillman use N ₂ O for substance abuse (acute alcohol withdrawal) [33]
1983-1985	PAN	Gillman and colleagues, examine N ₂ O in psychiatry (anxiety, depression and schizophrenia) [11-13, 78]
1984-1985	PAN	Gillman <i>et al.</i> use N ₂ O to investigate various neurological conditions (akathisia, Tourette syndrome, torticollis) [62, 68, 71]
1986	PAN	Gillman publishes conclusive evidence that N ₂ O is a multi-potent partial opioid agonist [14, 20, 88]
1988	PAN	Gillman and colleagues propose that the EOS is on final common pathway for all addictive drugs [42, 45]
1994	PAN	Daynes & Gillman confirm N ₂ O decreases withdrawal symptoms from other addictive substances apart from alcohol (nicotine, cannabis) [40]
1989	PAN	Lichtigfeld & Gillman demonstrate a strong placebo response in alcohol withdrawal treatment [47]
2001	PAN	De Wet <i>et al.</i> ameliorate hyperactivity with N ₂ O [76]
2002/2004	PAN	Gillman & Lichtigfeld publish double-blind studies demonstrating N ₂ O ameliorates acute alcohol withdrawal [37, 46]
2015	Fixed-50% N ₂ O:50%O ₂ *	Nagele <i>et al.</i> reawaken interest in using N ₂ O in depression [5].

Legend: Only the key events are listed, corroborative research can be found within the main text.

*Note any concentration of N₂O from 50% upward produces considerably more side effects including nausea, vomiting, pre-anaesthetic excitation and even anaesthesia, which is avoided by using the titration technique plus nasal mask *i.e.* PAN [3, 4, 28].

Abbreviations: PAN = Psychotropic Analgesic Nitrous oxide; EOS = Endogenous opioid system.

Numbers in square brackets refer to reference numbers referred to in the text.

The next crucial milestone in the history of N₂O, and indeed mankind, was the discovery of anaesthesia, by a dentist, Horace Wells. The discovery took place in 1844, years after Davy's book first appeared. In that year, Wells realised that the gas could be used as an anaesthetic and allowed the extraction of one of his own molar teeth under N₂O anaesthesia [2]. He thus introduced mankind to the boon of anaesthesia [2, 8, 9].

Another important pioneer was a physician of Polish extraction, Stanislav Klikovich, who worked in greater Russia.

For his MD thesis, he researched the potential medical applications of N₂O mixed with sufficient oxygen to avoid hypoxia, unconsciousness or anaesthesia. He received his MD in 1881 [10]. Much of his thesis was later published as a book describing the use of N₂O plus oxygen for assisting with angina pectoris, asthma as well as for obstetrics. During parturition, he also noted one of the important psychotropic properties of the gas *i.e.* anxiolysis, in addition to its analgesic effects. His important contribution apart from its use in obstetrics was to introduce the use of gas mixtures containing enough oxygen to avoid hypoxia and anaesthesia. None-

theless, apart from obstetrics, his other discoveries with non-anaesthetic mixture were not followed up to any notable extent [10].

3. MODERN ERA – 20TH AND 21ST CENTURIES

As will be seen, the early modern era of investigations into the neuropsychiatric effects of N₂O involved high anaesthetic concentrations, even when oxygen was added to the mixture. It was only in the 1980's that the safer, lower non-anaesthetic concentrations, usually below 40% N₂O (diluted with 60% or more oxygen) began to be used to research the neuropsychiatric applications of the gas [1, 3, 11-15].

The seminal work with N₂O, specifically for neuropsychiatric applications, was conducted by Julius Zador in 1928 [9]. For his researches, he used high anaesthetic concentrations of the gas diluted with some oxygen, although the amount of oxygen is not recorded. The N₂O was administered with a 'Zaaijer-Meißian' dental *anaesthetic* machine, via a facial mask. Since the vast majority of the patients received the gas at a dental clinic, it seems that they were seated in a dental chair while breathing the gas. All patients were anaesthetised and their response was observed during induction, during anaesthesia and for a short time afterwards. Gas exposure was usually 2-3 minutes.

The psychiatric study involved a mixed group of patients comprising 15 depressives, 36 schizophrenics (22 catatonic and 14 non-catatonic). Among the depressed patients, the N₂O lifted the reactive depressions while having a little beneficial effect on the endogenous type. Gas administration to the catatonic patients had little effect except some relaxation. Generally, the gas seemed to benefit the non-specific symptoms of schizophrenia, while aggravating the underlying schizophrenic process [9].

Zador also examined 24 patients suffering from various neurological conditions. These included 15 cases of post-encephalitic Parkinson's disease, 7 with Huntington's chorea and one each of athetosis and essential tremor [9].

In postencephalitic Parkinson's, he noticed that the tremor disappeared during all phases of gas administration, but the rigor although reduced, remained. Among Huntington's chorea and athetosis, there was only a quantitative influence on the number of movements. In the single case of essential tremor, the tremor in the extremities disappeared during induction and unconsciousness and reappeared within a few minutes of recovery [9].

Some years after the appearance of Zador's pioneering work, Fogel *et al.* [16] used pure anaesthetic N₂O in acute and chronic schizophrenic patients. Here, the suffocating actions of N₂O were exploited. The gas was applied until the patients' pupils were dilated, with the aim of producing cerebral hypoxia. This somewhat dangerous regimen appeared to improve early cases but had little effect on more chronic patients. They also mention that immediately *after* the gas administration patients reported a brief period of euphoria. The rationale for the use of the gas was not the actual properties of the gas but rather its ability to produce cerebral anoxia.

In 1944, Rogerson [17], used anaesthetic concentrations of the gas mixed with 45% air (or less) as a diluent, where

the patient self-administered the gas until immediately before falling unconsciousness. Once again, hypoxic concentrations were used to aid with psychotherapy in order to produce an abreaction. The abreaction often allowed the patient's repressed memories to surface and be recounted.

A few years later, more research was published by Lehman and Bos [18]. These workers, once again exploited the pure gas to produce cerebral anoxia. However, it is worth noting, that N₂O was chosen as an anoxic agent because 'the psychological after-effects were '.... preferable to, those produced by...pure nitrogen.'[18]. The cohort of patients examined was suffering from a large variety of different psychiatric conditions including anxiety states, manic-depressive illness, depression, alcohol and drug addiction and chronic schizophrenia. Most patients lost consciousness and became cyanotic after approximately 1 minute. They were immediately revived with pure oxygen with the average N₂O exposure lasting 3 minutes. Although the psychotropic effects of the gas itself were not investigated per se, the authors mention that patients frequently had 'vivid dreams' although they were often unable to remember the actual dream. Immediately after receiving the gas, most of their patients mentioned that they had a feeling of 'well-being' which lasted for a few hours after gas administration. The authors are careful to note that this 'well-being' was clearly different to the euphoria that often occurred during the induction phase and before full unconsciousness supervened. Most patients said that they felt more 'cheerful and vigorous', while manic patients felt more composed. Like Rogerson's patients, many were able to discuss or even re-enact a traumatic event. They were also often able to obtain a better insight into their illness during the period immediately after recovering from the anaesthesia. Following N₂O treatment, some patients, who usually required heavy night sedation for sleep, often slept well without medication. Presciently, these authors speculate on the notion that the gas acts by a specific pharmacological mechanism. They based their idea on the difference in 'psychological after effects' following N₂O hypoxia as compared to pure nitrogen hypoxia [18]. Of course, we now know that N₂O does indeed act via various neurotransmitter systems including the endogenous opioid and NMDA systems [1, 19-21]. Indeed, N₂O (and not Nitric Oxide [NO] as is commonly and erroneously believed [22]) was the first gas shown to have a roll in neurotransmission [14, 23, 24].

In other research, although not a systematic study of the actions of the gas per se, some workers compared ECT on its own with ECT plus succinylcholine, ECT plus thiopental or either thiopental or N₂O alone [25]. The various treatments were provided three times a week until 20 treatments had been given [25]. N₂O alone, at a concentration sufficient to cause unconsciousness, produced the best improvement for the schizophrenics, while it was third best after ECT alone or ECT plus succinylcholine for the relief of depression.

4. FROM 1970 TO PRESENT

As with anaesthesia [8, 9], dentists were the first to exploit the psychotropic properties of N₂O, at non-anaesthetic doses using continuous flow [26]. By the 1950's, many dentists were using it, not for its anaesthetic actions, but mainly for the gas' anxiolytic action [26]. Up to then, like the medi-

cal profession, it had largely been used at high anaesthetic doses [2, 3]. The only real exception were obstetricians, who have used it practically non-interruptedly from the time of Klikovitch [10, 27], mainly for its analgesic properties [27]. The gas is usually self-administered, intermittently during uterine contractions [27]. However, dentists led by exploiting one of N₂O most striking psychotropic properties, anxiolysis [3, 26, 28]. Analgesia was not the aim, because they used local anaesthesia for pain control [26, 28]. They clearly understood non-anaesthetic N₂O held many advantages for their patients (and themselves) by reducing patient anxiety [3, 26, 28].

In modern dentistry, for safety, N₂O is always mixed with at least 30% oxygen and titrated for maximum anxiolytic efficacy to doses rarely exceeding 40% [3, 28]. Nonetheless, higher doses are very occasionally used, but only for the rare hypo-responder [3, 28].

In dentistry, to exploit the gas' anxiolytic properties, a nasal mask, rather than a full facial mask, is always used [26, 28]. Another advantage of using a nasal mask (apart from the obvious operative reasons in dentistry) is that it increases the margin of safety, by allowing the patient to breathe air [26, 28]. It also avoids the trapped feeling and accompanying anxiety that may attend the use of a full anaesthetic facial mask, particularly if strapped to the face [4, 5]. A nasal mask, as opposed to a fixed facial mask, produces a much more open system and ensures that the actual concentrations breathed by patients are merely 30-50% of those indicated by the rotameter [29].

Rotameter concentrations of less than 50% are important for maximum anxiolysis because Malamed stipulates that more than 80% of subjects are suitably sedated and relaxed at doses not exceeding 40%. Indeed, approximately 95% of all subjects require less than 50% [28]. For this reason, a titration technique is chosen and the use of fixed concentration of 50% N₂O with 50% oxygen are discouraged, to avoid unnecessary oversedation (including anaesthesia) and other unpleasant side-effects [3, 4, 28].

As must be clear, most subjects require concentrations of N₂O, mixed with *more* than 50% oxygen for the optimal psychotropic effects and so as to avoid and/or minimise unpleasant side-effects [3, 26, 28]. These doses of N₂O below 50% (provided a nasal mask is used) limit nausea and vomiting and avoid over-sedation and/or anaesthesia [3, 4, 11-15, 28, 30]. The importance of avoiding a facial anaesthetic mask is obviously crucial for safety and efficacy. Indeed, 22% of subjects given a mixture of N₂O (30% diluted with oxygen) in oxygen for 30 minutes, via a facial mask, were nauseated and one vomited [30], indicating the problem of giving even these relatively low concentrations of gas through a facial mask as opposed to the nasal masks favoured in dentistry and by others who have investigated the neuropsychiatric actions of the gas [1, 3, 4, 13, 14, 26, 28-30].

However, it was only in the 1980's that the low-dose dental titration technique was studied for its potential usefulness to investigate and treat psychiatric conditions, including substance abuse [1, 11-15]. In 1994, the term psychotropic analgesic nitrous oxide (PAN) was introduced to clearly distinguish between anaesthetic doses used for anaesthesia and non-anaesthetic psychotropic concentrations obtained in den-

tistry by using the low-dose titration method with a nasal mask [14]. All of the research on PAN was premised on the notion that the gas had opioid properties [1, 14, 19, 20].

The first recorded occasion that N₂O was used in psychiatry, where unconsciousness was not the goal, appeared in 1970 [31]. The author reported that a premixed 50:50 mixture of N₂O and oxygen given *via* a full-facial mask aided psychotherapy. Unsurprisingly, this mixture occasionally produced unconsciousness, as it was administered by a facial mask [30]. The author, MacDonald, noticed that it was particularly helpful among patients, who were usually too inhibited and tense to co-operate. In these cases, the gas eased verbal psychotherapy. These finding replicated those of Rogerson, who used anaesthetic concentrations [17]. He also reported that it was useful as 'a desensitisation' technique 'for phobic and obsessional patients.' MacDonald also noted that recovery was extremely rapid and much quicker than other agents used as psychotherapeutic aids [31].

The first case of substance abuse, since the time that Humphry Davy effectively treated his own hangover with N₂O [7], occurred in 1972. Here, a fixed equal parts mixture of N₂O and oxygen was given [32]. The patient was a 41-year-old female, who suffered severe chronic pain which responded only partially to daily (700mg-1gm) pentazocine. Pentazocine had been given over an 18 month period. She was then exposed daily to a premixed mixture of N₂O 50% (plus oxygen 50%) for the initial 6 weeks, for 18-24 hours/day. For the remaining 202 days, she received the gas mixture for 6hrs daily. This regimen not only controlled her pain but allowed her to be successfully weaned off the pentazocine addiction and to resume relatively normal social function [32].

The earliest research, using PAN (*i.e.* the low-dose dental titration technique) in psychiatry was published in 1982. Here, in an open trial of 98 chronic alcoholics, the gas seemed to offer a rapid and safe relief of symptoms following mild to moderate alcoholic withdrawal states [33]. The positive response was believed to be, at least partially, due to the opioid properties of N₂O [33]. These authors noted that in many patients, the symptoms of depression were also lifted by the gas [33]. Another study by an independent researcher, also found that the gas treatment was effective for alcohol withdrawal across various ethnic groups [34]. A further study showed that PAN could be successfully and safely used in an outpatient setting [35].

The efficacy of the gas and its advantage over the benzodiazepines for alcohol withdrawal was also demonstrated in double-blind studies [36, 37]. More recently, two reviews suggest that PAN may show promise as an alternative to the benzodiazepines for treating alcohol withdrawal [38, 39]. After a cohort of patients had been successfully treated with PAN, a study showed the gas had marked anti-craving actions by preventing desire for alcohol, nicotine and cannabis [40].

Further research with PAN demonstrated that other forms of substance abuse including cocaine, methaqualone (Quaalude) mixed with cannabis (so-called 'white pipe', a form of substance abuse localised to South Africa) [41], nicotine [42, 43] and opioids [44] were also be ameliorated. As a result of the wide range of acute withdrawal states that could be rap-

idly improved with N₂O, it was suggested that the endogenous opioid system was on the final common pathway for all substances abuse withdrawal states [42, 45].

As noted in many of the reports on the researches with PAN, the efficacy of the gas are extremely technique sensitive and probably related to its action via the opioid and possibly other neurotransmitter systems, particularly at low doses [14, 44]. For this reason, workers not using the PAN dental method and thus, almost invariably using higher concentrations of N₂O failed to confirm the earlier findings [46]. Of course, Humphry Davy was the first to record the positive actions of the gas for alcohol withdrawal after he, himself, had overindulged [7].

Interestingly, a serendipitous finding during the study of PAN for alcohol withdrawal was a marked placebo effect [33, 47], which could be separated from the actual pharmacological actions of the gas [48]. As mentioned earlier, most of the work done by these workers was predicated on earlier findings indicating that N₂O acted on the endogenous opioid system for its effects [1, 14, 19, 49-52].

The first publications identifying the possibility that PAN might be more generally applied as an investigative, diagnostic, and therapeutic tool of the endogenous opioid system [12, 53] appeared in 1983 [54]. The study examined the effects of PAN on sexual arousal (measured by a subjective rating scale) in a group of women (n=7) as compared with compressed air, double-blind. It was found that compared with air, PAN enhances sexual arousal. The enhancement of sexual excitement in females has also been reported by other workers [55]. 4 of these subjects volunteered for the naloxone leg of the trial in which they masturbated to orgasm. It was found that an intravenous bolus injection of naloxone, when administered immediately prior to the onset of orgasm, could either inhibit or enhance orgasmic pleasure. Taken together with the enhancing effect of N₂O on sexual excitement it was concluded that the endogenous opioid system was involved in the human sexual response. Some years later, the latter finding was confirmed by other workers who also found that naloxone could influence human orgasmic pleasure [56]. An incidental finding was that 2 of the 4 women who received naloxone were unaware of their multiorgasmic potential, until this trial, indicating the possible use of PAN and naloxone in the treatment of sexual dysfunction [54]. The study also showed that PAN, apart from its efficacy for treating alcoholic withdrawal states, had potential investigative and therapeutic usefulness in an area other than substance abuse.

A speculation made in this paper was that owing to the biphasic action of naloxone on orgasm the same dual system (both opioid; the one pain-producing and the other pain-relieving) was also involved in pleasure production [54]. The opioid pain-producing system had been uncovered in earlier pain-related studies [51, 52] Thus, these findings indicated that pain and pleasure are on a physiological continuum, linked by at least one system *i.e.* the endogenous opioid system. An idea that was invoked more recently, by other workers [57-60]. Even more recently, research has pointed to another pleasure state, in this case, laughter, where the endogenous opioid system is also involved in a pleasure state [61].

Not long after N₂O, in the form of PAN, and naloxone had been used to study sexual response it was used to inves-

tigate a neurological condition, in this case, neuroleptic-induced akathisia [62]. By then, N₂O had been incontrovertibly shown to have opioid properties. As a consequence, the rationale for using PAN as a safe opioid probe of the endogenous opioid system directly in human neuropsychiatry had been clearly established [1, 14, 19, 20, 44, 63] (for a comprehensive list of references attesting to the opioid properties of N₂O see [44]). Nonetheless, one needs to recognise that the gas, like other opioids including the prototype morphine, also affects other neurotransmitter systems [1, 20, 64].

The long history of the use of opioids in psychiatry further supports the notion that N₂O produces its psychotropic actions via opioid actions. For example, from the 17th century onwards, opioids had been used to treat various psychiatric conditions including depression, psychosis and delirium tremens [65, 66]. The latter review articles, add further weight to the rationale for using low-dose, non-anaesthetic concentrations of N₂O (as a gaseous opioid) to investigate and treat the endogenous opioid system directly in man.

In 1984, when the opioid properties of N₂O had been firmly established [20], two patients suffering from neuroleptic-induced akathisia were studied to investigate a possible role for the opioid system in a neurological condition [62]. The first patient was given an intravenous bolus injection of naloxone with no improvement. In the second case, PAN was administered with immediate improvement in the patient's condition, which lasted for 6 hours [62]. The authors concluded that the opioid system was underactive in neuroleptic-induced akathisia. Soon afterwards, other researchers provided further evidence of opioid under-activity in neuroleptic-induced akathisia by showing that propoxyphene improved the disorder, while naloxone, used in a single case, exacerbated the condition [67].

Some other research, also in 1984, tested PAN's usefulness as an opioid in Tourette syndrome. PAN and naloxone were applied to a 31-year-old patient suffering from Tourette syndrome [68]. The patient had a 25-year history of recurrent episodes of the syndrome that had resisted treatment with a wide array of medications including propranolol, clonidine, carbamazepine, pimozide and diazepam. He was given PAN, which relieved his symptoms after 15 minutes. An intravenous bolus injection of naloxone reversed the improvement. These results indicated that the endogenous opioid system was likely to be involved in the pathogenesis of Tourette syndrome [68], a notion supported by later work [69, 70].

In 1985, PAN was given to a woman who suffered with idiopathic spasmodic torticollis; the gas produced a beneficial effect, indicating a possible under-activity of the opioid system in the condition [71]. It is therefore significant that torticollis was discovered in a cohort of patients suffering from neonatal abstinence syndrome, the majority of cases of which were opioid-induced, and the remainder polydrug induced (which may have included opioids) [72]. These observations strengthen the notion that underactivity of the opioid system is involved in the pathogenesis of torticollis.

Lichtigfeld and Gillman reported their findings with PAN in a range of psychiatric conditions, in 1985 [12]. A positive response was found in the following conditions: alcohol and opiate withdrawal states, post-alcoholic depression, reactive depressions some acute and chronic anxiety states. Low-

doses of the gas acted positively on the non-specific symptoms of schizophrenia, while higher doses worsened the symptoms. Higher concentrations of the gas (of approximately 50% or more) aggravated endogenous depression, particularly the psychotic type as well as the symptoms of acute schizophrenics. Non-responders included severe acute and chronic anxiety states, some highly withdrawn schizophrenics, particularly chronic cases, endogenous depressions as well as intractable depressions of all types. Some of these findings seem to support the pioneering observations of Zador [9].

At this juncture, we need to note an important caveat. There is a problem when comparing observations from earlier research with N₂O [9, 16-18, 31] with those of later work with PAN [12, 13, 33]. The earlier research used anaesthetic or near anaesthetic concentrations of N₂O [9, 16-18, 31]. Anaesthesia per se [73, 74] and pre-anaesthetic excitation associated with N₂O [3] are stressful. On the other hand, PAN is anxiolytic and anti-stress [3, 26, 28], despite interacting with discrete neurotransmitter systems [20, 21]. Unfortunately, as regards the earlier anaesthetic research, it is not possible to attribute to what extent the therapeutic action of N₂O was due to its pharmacological actions or to what extent it was due to the stress of anaesthesia [73, 74].

Also in 1985, the opioid action of PAN was used to investigate the role of the endogenous opioid system specifically in depression [13]. A cohort of alcoholic patients (n=25) was assessed for depression during and after treatment with PAN for their alcoholic withdrawal state. Another group, of depressed non-alcoholic subjects (n=25), was also evaluated before and after treatment with PAN. The depression in all the alcoholic subjects responded positively to PAN as did that of 21 non-alcoholic depressives. In all cases where the PAN was antidepressant the therapeutic effect occurred almost immediately. An unexpected finding was that the antidepressant action of PAN lasted for hours to days in 17 responders. Another finding mentioned was that depressed subjects (n=10) who were given PAN weekly maintained their confidence (of a positive outcome) during the latent period usually found with orthodox antidepressant medications [13]. Not long after, a psychological study also reported an enduring anti-depressant action of N₂O [75]. Although their subjects were conscious during gas administration it is unclear exactly how the gases were administered or at what concentrations [75].

In 2001 an open pilot, study of the effects of PAN on ADDH (attention deficit disorder with hyperactivity) on 10 children (age 9-13 years) was conducted [76]. The children were given titrated low-dose N₂O on up to 4 sessions over a two week period. Half of the patients responded positively, of which 2 relapsed. However, these recidivists once again responded positively to the gas [76]. These findings also support an endogenous opioid involvement in ADDH.

Another publication appeared in 2003 [77] detailing psychiatric research, originally conducted in the early 1980's and which was accepted and published as a DSc thesis in 1984 [78]. A pilot study of 24 cases were given N₂O using the low-dose PAN dental technique, (where the minimum concentration of oxygen was always at least 30%) until the depression lifted or was unaffected. In recalcitrant cases (n=4) up to 70% of the gas had no effect. Gas exposure

lasted between 20-30 minutes [77]. At the time, the responders fell into the diagnostic category of reactive/or neurotic depression while the non-responders had been diagnosed as endogenous depressions. Using more up-to-date psychiatric nosology it is feasible that some of the responders might have fitted into the category of endo-reactive or unipolar depression. At the time the work was originally done, in view of the positive response to PAN in most cases, it was postulated that those suffering from depression had an underactive opioid system [77, 78]. Much earlier work showing the efficacy of opioids for depression [65, 66, 79] as well as subsequent research [5, 80-82] adds further weight to the notion of an underactive opioid system in depression.

Since 2015, the interest in the potential of using N₂O for treating depression has resurfaced. Presumably, for convenience, these investigators chose to use a non-titration method with a relatively high fixed dose of the gas (50% N₂O diluted with 50% oxygen) via a facial mask strapped to the subjects face [5]. In this study, 20 depressed patients were exposed to N₂O administered for an hour. They were assessed after 2 and 24 hours on the 21-item Hamilton Depression Rating Scale (21-HDRS) and Quick Inventory of Depressive Symptomatology Self Report (QIDS-SR) scales.

They found that their subjects showed a significant improvement on both the 21-HDRS and QIDS-SR scales at 24 hours, however significant improvement on the QIDS-SR was seen only after 24 hours.

The authors [5] claim that their study was double-blind. Although precautions were taken to keep the study double-blind, it is virtually impossible that patients given placebo (50% oxygen in nitrogen), would not almost immediately recognise the difference in physical sensation between the placebo and 50% N₂O [3, 26, 28, 30]. It is well-known that the gas starts influencing consciousness and bodily sensations literally within minutes of inhalation, and certainly within 3-5 minutes [3, 28, 30]. The authors themselves agree that blinding is difficult, which they associate only with the euphoric actions of the gas [5]. However, even without euphoria other subjective and objective changes are so obvious that they are virtually impossible to ignore [26, 28, 30]. These clear changes occur even at the lower doses consistent with the dental titration method (with a nasal mask) and are therefore even more marked at the high 50% concentration via a full facial mask [28, 30]. It was for this reason that designing a true double-blind trial of N₂O against diazepam (for alcohol withdrawal) was so challenging [37]. The unpleasant adverse effects reported by these authors themselves with the 50% N₂O in oxygen (via a full-face mask) included nausea and vomiting, anxiety, panic attacks and regurgitation [5]. Nonetheless, the authors claim that these adverse effects were merely moderate to moderately severe and that it was worth taking the potential risk of subjecting their patients to these unpleasant side effects [4, 5]. However, it is an open question whether psychiatric patients should be subjected to any readily avoidable risk of unpleasant untoward effects, even if merely moderate [4]. Particularly, since most of these recorded problems [5] could have been side-stepped if the dental titration technique had been employed [4]. With PAN, the correct dose of N₂O is applied to each patient, minimising or avoiding any discomfort [4]. The titration method avoids oversedation and/anaesthesia and is also more rational

because the dose is tailored to each patient's needs [3, 4, 26, 28]. Nonetheless, despite the drawback of the method used [5], most of the patients benefited rapidly and the antidepressant effect lasted for 24 hours. Thus, these findings confirm both the antidepressant actions of the gas [9, 12, 13, 75, 77, 78] as well as the lasting effect noted by earlier authors [13].

These investigators suggest that the antidepressant actions of N₂O are mainly mediated by blockade of NMDA receptors [5, 83]. However, the available evidence does not support their contention. While NMDA receptors may have some role in the antidepressant properties of the gas, it is much more likely that the opioid action is responsible [4], as suggested previously [12, 13, 15, 77]. Particularly as they themselves [5, 83] are unable to explain a clear-cut discrepancy [4]. They note that while N₂O and ketamine both have a notable influence on NMDA [5, 21, 83] and opioid receptors [14, 19, 20, 84, 85] and are antidepressant, memantine which acts at NMDA receptors but lacks significant opioid receptor activity [86] is not antidepressant [5, 83].

More recently, some workers from the same laboratory [5] reported at a symposium on a neuroimaging study of the antidepressant actions of N₂O, using 0%, 25% and 50% double-blind [87]. They mention that they were able to detect changes in 3 neural networks related to the gas, but the actual changes are not detailed in the abstract. These investigators further reported that the gas showed antidepressant properties [87] as reported previously [5]. They also mention that animal research shows that lower concentrations of N₂O may be effective. A result, they again seem to confirm earlier work showing that the safer lower dose dental (PAN) titration technique with N₂O was antidepressant in depressed patients [1, 11-13, 15, 33, 75, 77, 78].

CONCLUSION

These findings seem to indicate that the use of a 50% N₂O plus 50% oxygen mixture, although more convenient, increases the risk of untoward side effects [3-5, 14, 28, 29]. The safer, more rational dental titration method, in which PAN is given, with doses matched to the patients' needs seems preferable [4]; particularly from a patient comfort and safety perspective [3, 4, 14, 26, 28]. Furthermore, it seems many of the psychotropic properties of the gas are mediated by the endogenous opioid system [1, 12-14, 19, 20, 63, 88] although other neurotransmitter systems may be involved, like the NMDA receptor system [5, 4, 21]. However, the role of other non-opioid systems, and the extent to which they contribute to the psychotropic properties of N₂O, still remains to be established.

Although over 2 centuries have elapsed since the psychotropic properties of N₂O were first observed, it is sobering to think that we still know relatively little about these actions. Clearly, a great deal more research is needed to understand and maximise these properties for the betterment of mankind.

Over 40 years ago, when I first started studying this fascinating gas, I came across the words with which Humphry Davy concluded his book. These words seem as apt today as when I first saw them, and indeed, as when they were first written: 'Pneumatic chemistry in its application to medicine, is an art in infancy, weak, almost useless, but apparently

possessed of capabilities of improvement. To be rendered strong and mature, she must be nourished by facts, strengthened by exercise, cautiously directed in the application of her powers by rational scepticism [7]'.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

I have been researching the psychotropic properties of nitrous oxide for over 40 years. Since 2003, I have been a medical adviser to Sedatek, a South African company that supplies equipment for administering low concentrations of nitrous oxide in South Africa, predominantly among dentists. I own no shares in the company. This mini-review was funded by the author.

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