Old drugs, new medication

Viejas drogas, nuevos fármacos

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History has shown us in recent years how some compounds originally designed for medicinal purposes have ended up as part of the wide range of illicit drugs. Conversely, some synthetic drugs for recreational use have travelled in the opposite direction and are now part of the therapeutic vademecum.

The first case is the more common, with products for clinical use being used (and abused) for recreational purposes for their pleasant, stimulating, psychodysleptic or entactogenic properties. This has been happening with old acquaintances from the world of addiction since the time of morphine, originally an analgesic, which left more than 400,000 addicts at the end of the American Civil War and became a fashionable high-society drug in the late 19th and early 20th centuries. Subsequently, opioid analgesics followed the trail of morphine, also in terms of its power of abuse and addiction. This was boosted by a letter published in the New England Journal of Medicine in 1980 minimizing the addictive potential of opioid analgesics, which could have contributed to North America's epidemic of addiction to opioid analgesics (Guardia Serecigni, 2018). Something similar occurred with cocaine, also created as a product for anaesthesia and a common ingredient in elixirs and tonics early in the 20th century, which is now the second most widely used illicit drug in Europe (European Monitoring Centre for Drugs and Drug Addiction, 2019); or benzodiazepines, considered nowadays to be a "silent epidemy," with a significant part of the Spanish general population using them as prescription medicines (Blasco-Fontecilla, 2018).

In the second scenario, where drugs of abuse are found to have clinical properties, we should highlight cannabis, the most widely used illegal drug in the world, and whose incorporation into the therapeutic arsenal of oncology in recent years has not been without controversy (Hill, Palastro & George, 2019).

Today, however, we need to turn our attention to a substance that would be in a third category, given the fact that it has made the round trip: ketamine.

From its origin as an anaesthetic, in the mid-1960s of the previous century, and having joined the world of drugs of abuse in the late 1980s for its hallucinogenic effects, ketamine (as well as its enantiomer, esketamina) is making a strong return to the world of therapy after its antidepressant properties and ability to reduce the risk of suicide were discovered.

Ketamine is a non-volatile anaesthetic agent synthesized in 1962 and subsequently marketed for human and veterinary use. It is presented as a translucent liquid and is a

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fat-soluble derivative of phencyclidine (PCP). Ketamine is used clinically as a general anaesthetic and, being considered a mild anaesthetic, is used is more widely in pediatrics and geriatrics. In our field of psychiatry, it is one of the commonly used anaesthetics in electroconvulsive therapy techniques (Mion, 2017).

Its psychodysleptic characteristics were discovered after a large number of patients reported what they felt on emerging from anaesthesia, and the first to use it as a drug of abuse were in fact veterans of the Vietnam War after experiencing its effects in field hospitals. Subsequently, cases of abuse began to appear among health professionals (as happened with morphine and derivatives). Those professionals who used it reported that a dose much lower than for anaesthetic use produced a psychedelic experience of great intensity. However, recreational use did not become widespread until the mid-1990s, coinciding with a drop in the purity of the cocaine distributed in Western countries, and was associated with the culture of electronic music and "rave parties." The perception of low risk, its short duration of action (compared to other hallucinogens) and low price contributed to its rapidly spreading use (Gómez-Arnau & Dolengevich, 2015).

On the illicit market, ketamine can come in many other forms: colourless liquid, white powder (crystals), tablets or capsules, so its use is possible through different routes of administration: intravenous, intramuscular (liquid), rectal (liquid), nasal (powder), pulmonary "smoked" (powder) and oral (liquid, tablet, or capsules). The pharmaceutical preparation of ketamine presented in liquid form can be converted to powder by the simple method of 'baking' or 'cooking' over low heat. This process can be carried out in a microwave, an oven at 90-95 Cº, or simply over a water bath until the liquid evaporates. The resulting crystals (like large grains of salt) are then crushed to produce a finer powder suitable for sniffing. This may be sold as is or may also be converted into tablets.

It was in the last ten years that the potential of ketamine as an antidepressant drug in subanaesthetic doses began to be considered. The first study to suggest this possibility dates back to the year 2000 and is a small-scale double-blind trial with a reduced sample of 7 patients, based on theories pondering the role of glutamate in the etiopathogenesis of depression (Berman, et al., 2000).

Findings in the following years point to an antidepressant as well as a potential anti-suicidal effect of ketamine and, interestingly, many of the data come from observing the clinical effects of the drug in the context of its use as an anaesthetic in ECT (Goforth & Holsinger, 2007; Okamoto, et al., 2010).

These preliminary data have led the scientific community to design clinical trials whose results have recently begun to see the light. The data yielded by these studies show ketamine as a fast-acting antidepressant (hours), whose clinical effects include the reduction of ideation and therefore of risk of suicide shortly after receiving the ketamine infusion. These effects, however, are not long-lasting, and disappear within a few days of the experimental treatment ending. Most trials use ketamine in the form of intravenous infusions in hospital settings, which presents a problem if the treatment is to be generalized as it would be consigned to limited use in serious situations requiring either partial or total hospitalization (Han, et al., 2016).

Fortunately, once the rapid antidepressant effect and anti-suicidal potential of ketamine had been verified, the pharmaceutical industry took a step further to facilitate wider use of this therapeutic alternative by synthesizing an intranasal formulation, more accessible to everyday clinical use than intravenous infusions of ketamine such as esketamine.

Esketamine, an enantiomer of ketamine, and therefore antagonist of the N-Methyl-D-Aspartate (NMDA) receptor that regulates glutamatergic transmission, has been developed as an intranasal formulation for the treatment of resistant depression, achieving a rapid reduction of major affective symptoms, including suicidal ideation in patients with imminent risk of suicide. The onset of action is so rapid that positive effects of the drug have been observed in as little as two hours, and relevant clinical effects within just 24 hours of intranasal administration of a single dose (Slomski, 2019).

The results of clinical trials in which esketamine is used in addition to the patient's usual treatment indicate that, compared with placebo, intranasal esketamine achieves rapid improvement of depressive symptoms, including suicidal ideation, in depressive patients with imminent risk of suicide (Canuso, et al., 2018). The efficacy demonstrated in trials has resulted in its approval by the United States Food and Drug Administration (FDA) as an adjunctive treatment for resistant depression in March 2019 (Cristea & Naudet, 2019) and by the European Medicine Agency (EMA) in December 2019.

The drug's potential is such that its clinical development by the pharmaceutical industry continues to advance, with more than 30 clinical trials of esketamine (ten in phase III) currently underway for short- and long-term treatment of both resistant depression and depression with suicidal ideation (Source: clinicaltrials.gov). Table 1 shows the published results of some of these trials.

Thus, a new direction is opened in the pharmacological treatment of depression and suicidal behaviour. It remains to be seen whether this anti-suicidal effect is limited to the context of the treatment and improvement of affective disorders, or whether it is an intrinsic effect of the drug which would allow its use in the plethora of mental pathologies which carry an increased risk of suicide. Clinical research will presumably provide data in this regard in the coming years.

Let us then welcome a substance which was beginning to be demonized by its potential for recreational use and abuse, and to which the avatars of advances in psychopharmacology have assigned a promising role in the treatment

Table 1. *Published results of clinical trials in depression with ketamine and esketamine*

Drug	Reference	Pathology	Study time	Result
Esketamine, nasal spray	NCT02133001	Major depression and suicidal ideation	4 weeks	Improvement in MADRS score compared to placebo at 4 and 24 h. Improvement in suicidal ideation at 4 h.
Esketamine, nasal spray	NCT01998958	Treatment resistant depression	10 weeks	Improvement in MADRS score compared to placebo, maintained over duration of study
Esketamine, nasal spray	NCT02493868	Treatment resistant depression	16 weeks	Esketamine + antidepressant reduced the risk of relapse by 51% compared to placebo + antidepressant
Esketamine, nasal spray	NCT02417064	Treatment resistant depression	4 weeks	Improvement in MADRS score compared to placebo. No differences in efficacy observed between doses of 56 mg and 84 mg
Ketamine, iv infusion	NCT02094898	Treatment resistant depression	4 weeks	Remission of clinical picture at one and four weeks in 41% of patients
Ketamine, iv infusion	NCT00088699	Major depression	1 weeks	Ketamine improved depressive symptoms compared to placebo at 110 minutes and one week after treatment
Ketamine, nasal spray	NCT01304147	Major depression	24 hours	Improvement in MADRS score compared with placebo at 24 h.
Ketamine, iv infusion	NCT01920555	Treatment resistant depression	3 days	Improvement in HAM-D and MADRS scores after an infusion of 0.5 or 1.0 mg/kg of iv ketamine

Note. clinicaltrials.gov

of affective disorders, a substance which can help keep in check the mortal enemy of professionals serving patients with mental disorders: suicidal behaviours.

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Conflicts of interest

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