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THE NOVEL THERAPEUTIC APPLICATION OF KETAMINE IN THE CONTEXT OF ABUSE POTENTIAL AND LIABILITY: A CRITICAL ISSUE FOR OLD AND NEW DRUGS

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The novel therapeutic application of ketamine in the context of abuse potential and liability: a critical issue for old and new drugs – Elena Arzenton
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Dedicated to
Damiano, Elisa and Davide

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ABSTRACT

Ketamine is a glutamate N-methyl-D-aspartic acid (NMDA) receptor antagonist that was developed in the 1960s. It was synthesized as a replacement for phencyclidine, an anaesthetic which had a range of adverse effects. Like phencyclidine, ketamine was shown to be a potent 'dissociative anaesthetic' that produced profound analgesia and amnesia without any slowing of heart rate or breathing. However, patients often reported 'emergence phenomena' (e.g. delusions, hallucinations, delirium and confusion, and sometimes 'out-of-body' and 'near-death' experiences) when recovering from ketamine anaesthesia. In turn, these phenomena led to ketamine being withdrawn from mainstream anaesthetic use with adult humans. Ketamine is still used today in specialist anaesthesia, particularly paediatrics, veterinary anaesthesia and field medicine.

Ketamine has other important medical uses that should be clearly distinguished from its non-medical use. In fact, ketamine also has a role in pain management, it has been used in intensive care management in cases of prolonged epileptic seizures, it is currently being researched in relation to heroin and alcohol addiction and it is used to explore the 'ketamine model' of psychosis. In particular, recent clinical studies showed that a single infusion of ketamine induced a rapid antidepressant response in subjects with Major Depression Disorder (MDD) and the discovery of such a novel action mechanism for the rapid treatment of MDD offers hope for treating resistant forms of depression. The unmet medical need for new antidepressants with a ketamine-like profile, i.e. a rapid onset of antidepressant action in resistant MDD patients, is now under intensive R&D scrutiny. However, the selection of candidates should also be based on an appropriate evaluation of undesired ketamine-like effects including reinforcing, sedative, psychotomimetic or stimulus properties. Thus, an early identification, characterization and description of ketamine adverse drug reactions (ADRs) in the population may be relevant, along with preclinical and clinical abuse liability studies as requested by regulatory agencies, in order to define the most appropriate compounds to be introduced in clinical practice. In fact, precisely those effects that limited the clinical use of ketamine made the drug appealing to recreational drug users and the recreational use of ketamine at sub-

anaesthetic doses has increased over recent years in many parts of the world and physical harm and addiction have been reported in heavy users. Initially confined to certain subcultures, ketamine is now the fourth most popular recreational drug among UK clubbers suggesting a high potential for abuse and it ranks among the most used drugs in urban settings in Asia.

The pharmacovigilance system may play a role in the identification and monitoring of how a drug is used in order to study its safety profile. Pharmacovigilance is defined by the World Health Organization (WHO) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects, or any other problem in the field of medicine". The monitoring of spontaneous suspected Adverse Drug Reaction (ADR) reports represents a key component of the integrated systems of pharmacovigilance. Furthermore, the latest European pharmacovigilance legislation amended the definition of ADR in order to comprise noxious and unintended effects resulting not only from the authorized use of a medicinal product at normal doses, but also from abuse, medication errors, misuse, occupational exposure, off-label use and overdose.

The main objective of this research project was to study how the data collected from pharmacovigilance reports can provide information on the use of ketamine as an antidepressant as well as on its abuse. A critical analysis was then carried out on the information obtained regarding ketamine in order to determine the contribution pharmacovigilance might offer in the context of abuse liability.

Clinical trials regarding the antidepressant use of ketamine were analysed in order to assess if there it was possible to carry out a systematic review and/or meta-analysis concerning the safety of ketamine as an anti-depressive. The ADRs reported in fourteen studies were considered, but, unfortunately, these were described or reported in different ways or not reported at all. For this reason, it was impossible to carry out a systematic review or meta-analysis.

The second analysis took into account the reports in the WHO database in order to compare the safety profile of ketamine when used at sub-anaesthetic or anaesthetic doses. The reports were divided in two groups according to a pre-defined cut-off dose: ketamine dose $\leq$ 30 mg and ketamine dose $\geq$30 mg. The

sample populations of the two groups were very similar in terms of gender, age and the source of the reports and most of the ADRs in both groups were related to "psychiatric disorders" SOCs, followed by "nervous system disorders".

In order to obtain information regarding ketamine abuse, two analyses were performed. First of all, the database of the Italian Pharmacovigilance Network was analysed to assess the impact of the new definition of ADR. In the Italian reporting form, a "Section 7" was included and this made it possible to collect and the analyse the ADRs deriving from the improper use of a drug. Over the three years considered, "Section 7" had been completed in 5.6% of the total number of reports and with regard to the different categories relating to "Section 7", abuse/misuse was the most significantly representative category. In the Italian Pharmacovigilance Network there were 23 ADR reports in which ketamine was indicated as the suspected drug: 21 of these referred to the use of ketamine for anaesthesia and 2 referred to ketamine abuse. Only in one case was abuse/misuse indicated in "Section 7".

In the final section, the WHO database was analysed to detect the reports referring to ketamine abuse. Those reports in which at least one of the preferred terms referring to abuse/misuse was mentioned were selected and analysed. 202 reports were extracted; grouping the ADRs according to the appropriate System Organ Class, the apparatus most commonly involved was nervous system disorders, followed by psychiatric disorders and renal and urinary disorders.

In conclusion, the results of the research which was carried out for this thesis have shown that while there are various publications which concern clinical studies on the efficacy of ketamine as an anti-depressant, there are no data in the literature on its safety with the result that it is not possible to create a safety profile relating to either its short or long term use. However, the analysis of spontaneous reports which was carried out, even though a number of limits were identified, confirmed that even low doses of ketamine cause ADRs involving nervous and psychiatric disorders. On the other hand, post-marketing surveillance based on spontaneous reporting has not revealed any significant new information concerning the abuse of ketamine. In fact, even after the introduction of a new definition of ADR, reports of ketamine abuse in Italy and worldwide have not increased. Those

profiles which are noteworthy regard conditions which derive from abuse liability, even though the reactions reported are very few. In the area of pharmacovigilance, some further implementations are necessary in order to provide more support and more useful information concerning drug abuse liability.

1. INTRODUCTION

1.1 KETAMINE: PHARMACOLOGY AND USE

Ketamine (2-[2-chlorophenyl]-2-[methylamino]cyclohexanone) is a member of a group of compounds known as arylcyclohexylamines (ACMD, 2013; Wolff and Winstock, 2006). It was developed in the 1960s by Dr. Calvin Lee Stevens of Wayne State University for the pharmaceutical company Parke-Davis (Hillhouse and Porter, 2015). Parke Davis Laboratories developed ketamine as a replacement for phencyclidine (PCP, 'angel dust'), an anaesthetic which had a range of adverse effects such as aggressive behavioural problems and adverse psychological reactions (Figure 1) (Ashton, 1998; Morgan and Curran, 2011; Wolff and Winstock, 2006).

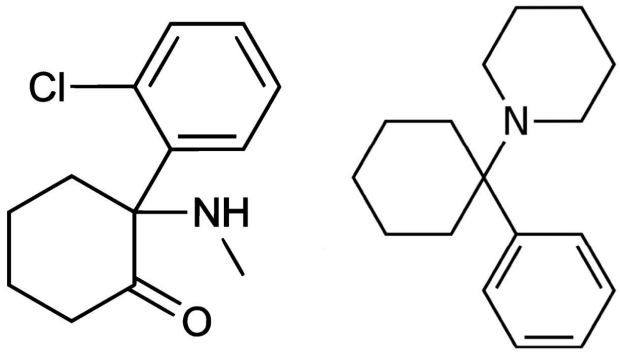

Figure 1. The chemical structures of ketamine (left) and phencyclidine (right) Ketamine and phencyclidine share a binding site within the pore of the NMDAR and induce similar effects. Both chemicals are dissociative anaesthetics and share structural similarities such as aromaticity. Image taken from Frohlich and Van Horn, 2014.

Ketamine was first introduced as a dissociative anaesthetic for injured American soldiers during the Vietnam War in 1964 (Domino, 2010). Despite its unusual clinical effect and the multifaceted mechanism of its action, ketamine has been employed in several areas of medicine, including paediatric analgesia and anaesthesia, obstetrics and the Emergency Department (Ellis et al., 2004; White et al., 1982). Moreover, thanks to its good safety profile (the relative preservation of

airway reflexes and haemodynamic stability; spontaneous ventilation; analgesia and sedation without loss of consciousness) has also led to it being the anaesthetic drug of choice in parts of the world that have limited availability of resuscitation equipment (Peck et al., 2008). Also in veterinary medicine, ketamine is the most widely used anaesthetic agent in all animal species. Its popularity in equine medicine is reflected in a common street name: "the horse tranquilliser" (Morgan and Curran, 2011; Reich and Silvay, 1989).

1.1.1 Pharmacokinetics

Routes of administration and dosing

Ketamine may be efficiently administered by different routes including oral, intranasal, intravenous, subcutaneous and intramuscular, all of which permit adequate absorption and excellent bioavailability (Jansen, 2000a). For analgesia, the intrathecal route is used as well. The oral, rectal (Marhofer et al., 2001) and transdermal routes have also been described (Azevedo et al., 2000; Reich and Silvay, 1989). Wolff and Winstock said that it's important to consider these various routes of administration of ketamine when assessing its abuse potential, as uncomplicated and innocuous modes of delivery may favour non-medical use (Wolff and Winstock, 2006).

The dosage of ketamine differs according to the reason for its use. For example, a dose equivalent to 2 mg of ketamine per kg body-weight given intravenously over 60 seconds usually produces surgical anaesthesia within 30 seconds lasting for 5-10 minutes (the dose may range from 1 to 4.5 mg/kg). An intramuscular administration of 10 mg per kg body-weight (range 6.5-13 mg/kg) usually produces surgical anaesthesia within 3 to 4 minutes lasting for 12 to 25 minutes (Reynolds et al., 1989). Instead analgesia is obtained by administration of 0.2-0.75 mg/kg intravenously (Reich and Silvay, 1989). Sub-anaesthetic doses inducing psychotropic effects range from 0.1 to 1.0 mg/kg i.v.. In clinical studies, this dose may be divided into a bolus of 0.1-0.2 mg/kg and a maintenance infusion of 0.0025-0.02 mg/kg/min (Krystal et al., 1994; Malhotra et al., 1996; Oranje et al., 2000; Vollenweider et al., 1997; WHO, 2014). Intramuscular administration of

ketamine in a dose range from 25 to 200 mg has been reported to produce psychotropic effects in humans (Hansen et al., 1988).

Adsorption and bioavailability

Ketamine is rapidly absorbable by intravenous, intramuscular, nasal and oral routes due to both its water and lipid solubility (Amiot et al., 1987; Grant et al., 1981; Kronenberg, 2002; White et al., 1982). Bioavailability is low for oral and rectal routes because of the first-pass metabolism in the liver and intestine. It reaches 17–20% through the oral route and 30% for the rectal route. The percentage for other routes is: 30% for the sublingual route, 93% for intramuscular and 25–50% for intranasal (Chong et al., 2006; Grant et al., 1981; Yanagihara et al., 2003). Peak plasma concentrations are reached within a minute intravenously, 5–15 min intramuscularly, and 30 min orally (Grant et al., 1981).

Distribution

Ketamine has a high lipid solubility and low plasma protein binding (12%) which facilitates rapid transfer across the blood–brain barrier. Initially, it is distributed to highly perfused tissues, such as the brain, heart and lungs, to achieve levels 4-5 times those in plasma (distribution half-life after i.v. within 30 sec.) (Wolff and Winstock, 2006). CNS effects subside following redistribution to less well-perfused tissues (re-distribution half-life, 2.7 min.) (WHO, 2014).

Metabolism and excretion

Biotransformation primarily takes place in the liver and multiple metabolites have been described. The most important pathway is N-demethylation to norketamine by the isoform CYP3A4 of the cytochrome P450. Norketamine is an active metabolite with an anaesthetic potency one third that of ketamine and it has analgesic properties. It may be metabolized through multiple pathways, but the majority is hydroxylated and subsequently conjugated to water soluble compounds that are excreted in the urine (Reich and Silvay, 1989; WHO, 2014).

1.1.2 Pharmacodynamics

The pharmacodynamics effect of ketamine in humans is apparently due to the Central Nervous System (CNS) activity of the parent compound. As CNS levels of ketamine decline by redistribution to the peripheral compartment, the CNS effects subside, although not as rapidly as would be predicted from its high lipid solubility (Clements and Nimmo, 1981). Decreased renal function and the presence of active metabolites, do not prolong the drug's action. Tolerance and hepatic enzyme induction have been reported following chronic administration (Reich and Silvay, 1989).

Ketamine is a potent analgesic at sub-anaesthetic plasma concentrations, and its analgesic and anaesthetic effects may be mediated by different mechanisms (Reich and Silvay, 1989). However, the complete pharmacology of ketamine is complex and it is known to directly interact with a variety of other sites to varying degrees.

Ketamine acts primarily as a non-competitive N-methyl-D-aspartic acid (NMDA) receptor antagonist and this is the most significant pharmacological action accounting for most of its effects. Specifically ketamine blocks NMDA receptors by binding to the open channel conformation of the N-methyl-D-aspartate (NMDA) receptor. It binds to a site within the calcium channel of this receptor, the so-called ‘‘PCP site’’, because it is also where phencyclidine binds. NMDA receptors are postsynaptic and activate long-term potentiation and synaptic plasticity (Figure 2) (Stahl, 2013). Due to the blockade of NMDA receptors on inhibitory gamma amino butyric acid (GABA) neurons in the prefrontal cortex, ketamine also results in a glutamate release downstream. In fact, if an NMDA receptor on a GABAergic interneuron is blocked by ketamine, this prevents the excitatory actions of glutamate there. Thus, the GABA neuron is inactivated and does not release GABA. GABA binding at the second cortical glutamatergic pyramidal neuron normally inhibits glutamate release: thus, the absence of GABA there means that the neuron is disinhibited and glutamate release is increased. This glutamate stimulates postsynaptic AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors that mediate fast, excitatory neurotransmission by allowing sodium to enter the neuron to depolarise it (Stahl, 2013).

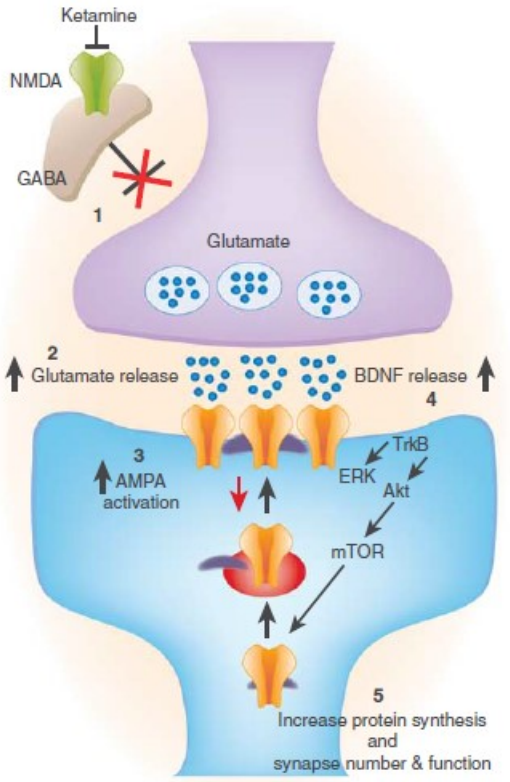

Figure 2. Proposed mechanism regarding the action of ketamine.
Ketamine, by means of blocking GABAergic inhibition (1), causes a surge in glutamate release and cycling (2). The resulting increased glutamatergic transmission by means of AMPA receptors (3) leads to increased brain-derived neurotrophic factor (BDNF)-dependent (4) levels of synaptogenesis (5) that ultimately contribute to rapid and sustained antidepressant effects. Image taken from Sanacora and Schatzberg, 2015.

Action at the NMDA receptor is considered to underlie the analgesic and dissociative effects of ketamine and to have important effects on memory (Wolff and Winstock, 2006).
A debate is ongoing as to whether it is the direct actions of ketamine at the PCP site on the NMDA receptor that account for its actions or the downstream stimulation of AMPA receptors. One hypothesis for why ketamine has antidepressant actions proposes that it is actually the stimulation of AMPA receptors and not the blockade of NMDA receptors per se that causes the antidepressant action (Li et al., 2010).

It is also well established that ketamine has effects on opioid receptors at central and spinal sites and noradrenaline (norepinephrine), serotonin and muscarinic cholinergic receptors elsewhere (Figure 3) (Kong et al., 2002; Nishimura and Sato, 1999).

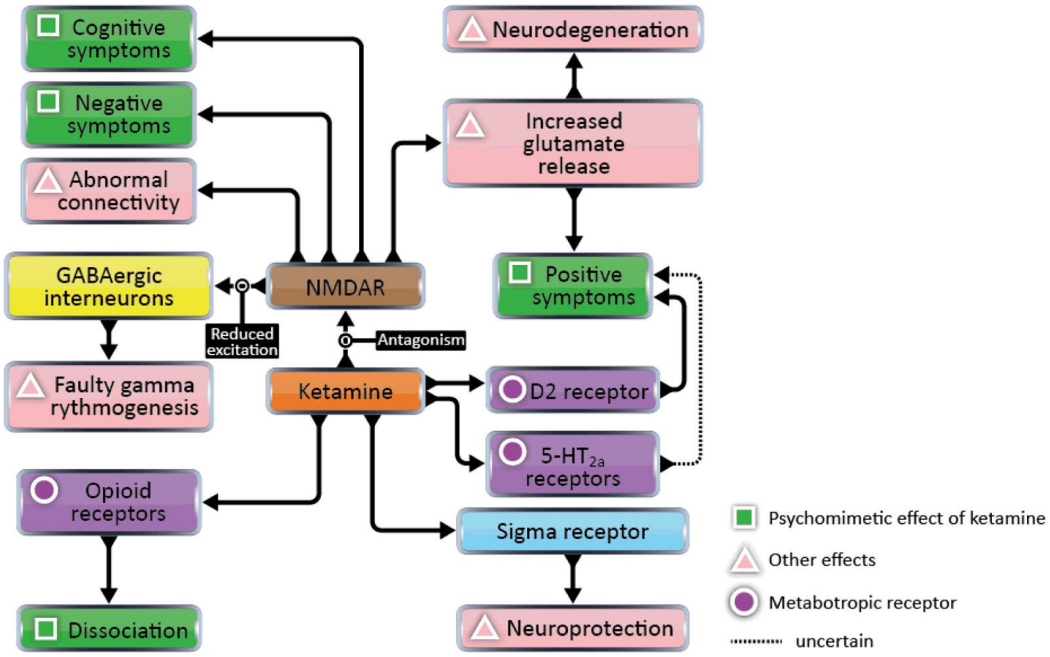

Figure 3. The various effects of ketamine on many receptors

Ketamine is a ligand of many different receptors. A map of causal relationships between receptors and the effects of ketamine is represented. Effects of D1 dopamine receptors and NMDAR may also converge to cause cognitive symptoms; however, only receptors that interact directly with ketamine are pictured here. Image taken from Frohlich and Van Horn, 2014.

It has also been found to significantly inhibit the uptake of noradrenaline, dopamine and serotonin in a dose-dependent fashion in human embryonic kidney cells. It has been postulated that the psychotomimetic and sympathomimetic effects are thus mediated through this enhancement of monoaminergic neurotransmission in the brain (Nishimura et al., 1998).

Additionally, several studies indicate that opioid receptors (α and μ) are also involved in the pharmacological effects of ketamine (Freo and Ori, 2002) and that the analgesic effect of ketamine may largely be attributed to the activation of these central and spinal receptors (Crisp et al., 1991).

1.1.3 Adverse reactions

Ketamine use is not without risks and, like all drugs, it can cause adverse reactions. The effects of the drug are influenced by various factors including the route of administration, the constitution of the individual and any other drugs consumed. It has a wide margin of safety in clinical practice but when used as an anaesthetic, patients have often described "emergence phenomena" such as delusions, hallucinations, floating sensations, delirium and confusion and sometimes 'out-of-body' and 'near-death' experiences. These phenomena are more common in adults (30-50%, with more females than males) than in children (5-15%), shorter operative procedures, and those receiving large doses, particularly when administered quickly (Bergman, 1999; White and Ryan, 1996). As a result of this, ketamine was withdrawn from mainstream anaesthetic use with adult humans. As mentioned previously, ketamine is still used today in paediatrics, veterinary anaesthesia and field medicine (Gao, 2016; Morgan and Curran, 2011; WHO, 2014). The symptoms described above were found to be reduced by concurrent use of benzodiazepines and making sure the patient is in a low stimulus environment. It is also advisable to provide pre-operative information on the possible emergence reactions (Strayer and Nelson, 2008).

Due to concerns that ketamine may potentially cause an increase in intracranial pressure, it is usually to be avoided in people with or at risk of intracranial hypertension (Wang et al., 2014). Other adverse reactions regard the cardiovascular system, including abnormal heart rhythms (slow or fast heart rate) and blood pressure variations (increase or decrease). In fact, it has been widely recommended that ketamine be avoided in patients with known or possible coronary artery disease, congestive heart failure, or hypertension (Green et al., 2011). Ketamine use is associated with a lower risk of respiratory depression; indeed, laryngospasm and apnoea are relatively uncommon and have essentially

always has been transient and have responded quickly to assisted ventilation and oxygen (Green et al., 2009; Green et al., 2011). Other non-serious reactions can be: pain or erythema in the injection site (dermatologic system); anorexia, nausea, increased salivation, vomiting (gastrointestinal system) and tonic-clonic movements (neuromuscular and skeletal system).

1.1.4 Other clinical uses

Ketamine has significantly expanded its therapeutic relevance since its first development and uses (anaesthesia and sedation) and it is now being used or studied in many other medical fields.

First of all, it has a role in pre- and post-operative pain management in both human and veterinary medicine. It is a potent analgesic and low doses of ketamine given before, during and after surgery improve post-operative pain relief (Morgan and Curran, 2011).

Most recently, ketamine has been used to treat various chronic pain syndromes, especially those that have a neuropathic component (Breadlau et al., 2013; Marchetti et al., 2014). Low doses (0.1–0.5 mg/kg/hour) of ketamine can be used for neuropathic pain states (Lynch et al., 2005) and is also effective in treating complex regional pain syndrome (Correll et al., 2004). However, the long-term effectiveness of ketamine for the treatment of chronic pain remains controversial and some studies demonstrate contradicting results (Amr, 2010; Barreveld et al., 2013;). Ketamine could be an alternative choice for the treatment of chronic pain in cancer patients who otherwise require a high-dose of opioids or for people whose other treatments are insufficient for analgesia (Schug and Goddard, 2014). However, in these cases too, further studies are needed to determinate the real effect and the optimal dose.

Ketamine has also been used in intensive care management in cases of prolonged epileptic seizures (Fujikawa, 1995).

Other potential clinical uses of ketamine are currently being researched (Aroni et al., 2009), particularly in the treatment of resistant depression (see next section) and in heroin and alcohol addiction (Krupitsky and Grinenko, 1997).

It is known that ketamine produces symptoms similar to those of schizophrenia and thus in some experimental studies, single doses of ketamine are used to explore the 'ketamine model' of psychosis (Domino and Luby, 2012; Fletcher and Honey, 2006).

1.1.5 Antidepressant use

Depression remains a leading cause of disability in the world, affecting an estimated 350 million people worldwide (Marcus et al., 2012), such that currently it is the eleventh highest contributor to global disability-adjusted life years (Murray et al., 2012). Despite its high prevalence and invalidity, treatment response and remission rates remain low. The usual antidepressant drugs are not adequate due to the long treatment time course required to reach full efficacy (weeks to months) and they have limited response in treatment-resistant patients (Insel and Wang, 2009). Currently, electroconvulsive therapy (ECT) is considered the most effective management of treatment-resistant depression, with a rapid onset of response and high remission rate. However, its use is restricted due to the risk of memory and cognitive impairment (UK ECT Review Group, 2003). Many depressed patients, especially those who are at risk for suicide, require an effective, fast-acting antidepressant. Therefore, there is a need to developing alternative treatment options for depression which have both a faster response onset and a higher success rate than current pharmacological and other physical treatment options (Katalinic et al., 2013).

Since the first placebo-controlled trial investigating the antidepressant effects of sub-anaesthetic ketamine doses in 2000 (Berman et al., 2000), interest has risen dramatically and a great deal of clinical research followed. Over the years, several studies have shown that a single intravenous administration of ketamine induced a rapid antidepressant response that lasted for up to 7 days in subjects with bipolar disorder (Diazgranados et al., 2010b; Ibrahim et al., 2011) or Major Depression Disorder (MDD) (aan het Rot et al., 2010; Diazgranados et al., 2010a; Machado-Vieira et al., 2012; Price et al., 2009; Zarate et al., 2006). Noticeably, ketamine acutely induces therapeutic effects similar to those observed after chronic administration of currently used antidepressants. The discovery of such a novel

action mechanism for the rapid and novel treatment of MDD offers hope for treating resistant forms of depression (Shelton et al., 2010). The unmet medical need for novel antidepressants with a ketamine-like profile, i.e., a rapid onset of antidepressant action in resistant MDD patients, is now under intensive R&D scrutiny. The selection of candidates should also be based on an appropriate evaluation of undesired ketamine-like effects, including reinforcing, sedative, psychotomimetic or stimulus properties (Burgdorf et al., 2013). Thus, the early identification, characterisation and description of ketamine adverse drug reactions (ADRs) in the population may be relevant, along with preclinical and clinical abuse liability studies as requested by regulatory agencies (EMA, 2006), in order to define the most appropriate compounds to be introduced in clinical practices.

1.1.6 Recreational use

As previously stated, reports of "emergence phenomena" have determined the withdrawal of ketamine from mainstream anaesthetic use in adult humans. However, it is precisely these effects that made the drug appealing to recreational drug users. The first reports of the non-medical use of ketamine appeared in the 1960s (Siegel, 1978); some suggested that its recreational use in North America may have been linked to returning Vietnam veterans who had experienced it on the battlefield (Dillon et al., 2003; Dotson et al., 1995). Ketamine remained rare in Europe until the 1990s when it appeared on the 'rave' and nightclub scenes, initially as an adulterant in ecstasy tablets (Dalgarno and Shewan 1996), but the recreational use of ketamine at sub-anaesthetic doses has increased over recent years in many parts of the world and physical harm and addiction have been reported in heavy users (ACMD, 2013; Morgan and Curran, 2011; Schifano et al., 2006). Initially confined to certain subcultures, ketamine is now the fourth most popular recreational drug among UK clubbers, suggesting high potential for abuse (Morgan and Curran, 2011) and it ranks among the most used drugs in urban settings in Asia (Joe-Laidler and Hunt, 2008; Ng et al., 2010). As a result of its increased recreational use, ketamine became a Schedule III non-narcotic substance under the Controlled Substances Act in 1999 (Drug Enforcement Administration, 2013; Hillhouse and Porter, 2015). Although diversion of use is

reported in healthcare and veterinary settings, in the case of recreational use, there are however no available data regarding the magnitude of the phenomenon according to the 2013 report from the British Advisory Council on the Misuse of Drug. Epidemiological data show a significantly decreasing trend in ketamine use (Home Office, 2013); on the other hand, there is a significant increase in people presenting themselves at emergency departments in the UK as a result of suspected toxicity (Wood et al., 2013). Ketamine is also known with "street names" such as Special K, jet, super acid, green, K and ''cat Valium" (Drug Enforcement Administration, 2013).

At sub-anaesthetic doses, ketamine may produce hallucinations (i.e. a distorted perception of sight and sounds), temporal and spatial distortion, mood and body image changes and feelings of being disconnected (or dissociated) from the body or from reality (i.e. "out of body" experiences) (Leary and Sirius, 1997; Wolff and Winstock, 2006). The duration of these effects is relatively short (approximately 30 to 60 minutes) as compared to phencyclidine and the hallucinogenic effects of ketamine have been termed the "K-hole" by users when it is taken in large doses. The term "K hole" refers to the place "where users are" when under the influence of ketamine (Drug Enforcement Administration, 2013; Hillhouse and Porter, 2015). Sometimes the "K hole" can reproduce the features of a "near-death" experience, including buzzing, ringing and whistling sounds at the beginning and a sensation of travelling through a dark tunnel into light at a high speed with intense visions (Leary and Sirius, 2004). Ketamine is also sometimes used in drug-facilitated sexual assault (i.e. as a date rape drug) (Anderson and O'Donnell, 2000; Smith et al., 2002;) and in sexual activities to enhance (Lim, 2003).

Ketamine is mainly obtained in a powder form and administered by means of snorting or inhaling. Other forms of ingestion include liquid injected intramuscularly or (rarely) intravenously. Ketamine is occasionally taken orally; by this route it is quickly metabolized to norketamine producing a more sedative and less psychedelic experience (Morgan and Curran, 2011). Testing for the presence of ketamine in an intoxicated individual is difficult because of its short half-life. Nevertheless, ketamine and its metabolites can be detected in plasma, hair and urine using gas chromatography, mass spectroscopy and high

performance liquid chromatography (Bolze and Boulieu, 1998; Wolff and Winstock, 2006).

Harm related to ketamine abuse

Nutt and colleagues developed a scale with three main factors that together define the harm associated with any drug of potential abuse such as ketamine (Nutt, 2007). This divides the damage associated with psychoactive substances into a matrix of nine under three broad categories, each with three subcategories. These comprise physical harm to the individual user caused by the drug itself (acute physical risks, chronic risks, the propensity for intravenous use); dependence-related harm due to the fact that there is a tendency for the drug to induce dependence (acute pleasure, risk of physical dependence, propensity for psychological dependence) and social harm such as the effect of drug use on families, communities and society (acute social harm due to intoxication, harm to the individual within society, costs to the health service) (Morgan and Curran, 2011).

In cases of acute toxicity, the adverse effects of ketamine may be delirium, amnesia, impaired memory, hyperthermia, impaired motor functions, cardiac risk (increased heart rate, cardiac output and blood pressure) and increased muscle tone (Morgan and Curran, 2011). Cerebral blood flow and intracranial pressure are increased (Klein and Kramer, 2004). Respiratory problems are minimized because there is no suppression of the gag reflex and coughing and swallowing reflexes are maintained (Morgan and Curran, 2011). Nausea and vomiting can occur, especially with first-time users (Dillon et al., 2003). Death from ketamine alone is rare. The highest mortality risk is related to the accidental deaths due to intoxication which causes dissociation and analgesia which may lead to a person harming them self (Jansen, 2000b; Stewart, 2001).

Other types of damage are related to the chronic use of ketamine. Many complications involve the urinary tract, documented for the first time in 2007 (Shahani et al., 2007). The symptoms described included frequency and urgency of urination, dysuria, incontinence and haematuria. Laboratory investigation (cystoscopy and biopsy) revealed ulcerative cystitis, oedema and denuded

urothelial mucosa. The most frequently affected area is the bladder but renal damage can also occur. In fact, unilateral or bilateral hydro nephrosis and renal failure may appear in frequent, high dose ketamine users (Chu et al., 2008).

Gastrointestinal problems include intense abdominal pain (K-cramps), gallbladder malfunction (e.g. biliary dilation) and hepatic toxicity (Poon et al., 2010). These symptoms abate with the cessation of ketamine use.

As mentioned above, psychological effects include out-of-body experiences, hallucinations and an altered sense of time (Bokor and Anderson, 2014). In some cases, there has been an increase in depression (Morgan et al., 2010) - which is in contrast with studies that suggest the use of ketamine as an antidepressant (Berman et al., 2000) - and cognitive impairment in both short and long term memory (Morgan and Curran, 2006).

Regarding dependence-related harm, pre-clinical studies (e.g. reinforcing efficacy in self-administration model) have revealed similarities between the reinforcing effects of ketamine and other addictive drugs (Klein et al., 1999; Morgan and Curran, 2011). Ketamine tolerance, that is, the need to administer increasing doses to achieve the same effect, has been demonstrated in children who have undergone anaesthesia (Abi-Saab et al., 1998). However, at the moment, there is limited evidence of a withdrawal syndrome but some potential symptoms include anxiety, dysphoria and tremors (Cheng et al., 2007).

Ketamine abuse causes severe damage to individuals and society (Morgan and Curran, 2011). One of the major concerns is driving under its influence which may lead to a fatal vehicle crash due to decreased attention and impaired memory functioning (Muetzelfeldt et al., 2008). Additionally, it has also been suggested that ketamine produces an enhanced sex experience, a factor which may encourage drug-facilitated sexual assaults (Bokor and Anderson 2014). Chronic ketamine use is also a cost to health services. The majority of the costs stem from chronic physical health problems (e.g. ulcerative cystitis) and follow-up visits. Furthermore, the treatment of ketamine dependence may represent another cost to society (Morgan and Curran, 2011).

1.2 PHARMACOVIGILANCE AND ADVERSE DRUG REACTIONS

1.2.1 Post-marketing surveillance and spontaneous reporting system

The name Pharmacovigilance relates to a number of activities designed to process all information concerning drug safety and to ensure, for all medicinal products, a favourable risk / benefit ratio for the population (Italian Medicines Agency, AIFA website). The realization that there was a need for this type of system resulted from the thalidomide disaster in the early 1960s that caused serious foetal deformities (phocomelia) when it was used as an antiemetic and sedative agent for pregnant women (McBride, 1961). In 1968, the World Health Organization (WHO) created the "Programme for International Drug Monitoring", a pilot project whose aim was to develop a system for the centralization of world data on adverse drug reactions (ADRs). In particular, the main aim of the "WHO Programme" is to identify the earliest possible pharmacovigilance signals (Olsson, 1998). The term "pharmacovigilance" was proposed in the mid-70s by a group of French pharmacologists and toxicologists in order to define the various activities promoting "The assessment of the risk of side effects potentially associated with drug treatment" (Bégaud et al., 1994; Mazzitello et al., 2013).

Post-marketing supervision of drugs is necessary as the pre-marketing testing limits. In fact, before marketing a drug is subjected to a series of studies mainly to evaluate its effectiveness. The duration of these studies is around 7-10 years and they are divided into a pre-clinical phase (in vitro and in vivo studies in animals) and a clinical phase. During pre-clinical studies, the pharmacokinetics, pharmacodynamics and in particular the toxicology of new substances are evaluated. The aim of clinical trials is instead to assess the efficacy of a new drug in terms of the indications for which it has been designed, in relation to what is already available on the market. In addition, information regarding the drug's safety and tolerability is also provided.

With regard to adverse drug reactions, pre-marketing studies have several limitations:

- a limited number of patients, making it impossible to discover rare adverse reactions;

- the population exposed to the drug is very different from the real population; For example, children, the elderly and polypathological adults or adults in polytherapy are excluded;
- the limited duration of the trials does not allow for the discovery of delayed reactions which can occur even some years after the suspension of the drug.

Post-marketing surveillance activities are therefore important as they bring to light any unexpected and/or serious ADRs (WHO, 2002b). The safety of a new drug cannot be established until it has been on the market for some years and it is not unusual for a drug to be withdrawn from the market following the identification of new adverse reactions. About 3% of new drugs are withdrawn from the market due to safety concerns during the first 5-10 years of use in the population. A further 5-10% of new drugs undergo variations in the Summary of Product Characteristics (Bakke et al., 1995; Lasser et al., 2002). Furthermore, ADRs have a high impact on public health and they represent a significant economic burden on the health system and society in general (White et al., 1999).

For this reason, it is clear that pharmacovigilance is extremely important and in fact it is defined by the WHO as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects, or any other problem in the field of medicine" (Vallano et al., 2005; WHO, 2002b). The monitoring of spontaneous suspected ADR reports represents a key component of the integrated system that is pharmacovigilance.

Pharmacovigilance has four main objectives (Edwards, 1997; Mazzitello, et al., 2013):

1. to recognize, as quickly as possible, any new ADRs;
2. to improve and increase information about already known or suspected ADRs;
3. to assess the benefits of one drug as compared to others or to other types of therapy;
4. to communicate the information gathered in order to improve therapeutic practice.

As stated earlier, the general aim of pharmacovigilance is to identify any alarm signals as early as possible by means of the early detection of new ADRs (Olsson, 1998).

In pharmacovigilance, a signal is defined as follows: “Information that arises from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, which would command regulatory, societal or clinical attention, and is judged to be of sufficient likelihood to justify verifiable and, when necessary, remedial actions” (Hauben and Aronson, 2009; Mazzitello, et al., 2013).

It must be stressed that the study of the risks associated with a drug is more complicated than that relating to its benefits mainly because, for example, ADRs are usually aspecific and serious ADRs are uncommon.

As part of the WHO Programme for International Drug Monitoring, databases have been created in Member States for the collection and evaluation of individual case safety reports (ICSRs) originating from spontaneous reporting system (Pal et al.,2011).

Spontaneous reports are communications regarding suspected adverse reactions after taking a drug. Physicians and other healthcare professionals are required to report suspected ADRs and patients can also report them. All reports are sent to a qualified person responsible for ADR report management who then inserts them into the database of the National Pharmacovigilance Network (Directive 2010/84/EU, 2010). Meyboom et al. comment that "The experience teaches that the spontaneous reporting system cannot be replaced by any other method in the identification of new adverse reactions" (Meyboom et al., 1997). As with other methodologies, it has some advantages and some disadvantages.

In effect, this spontaneous reporting method is simple, practical and economical and it is applicable to all types of patients and to all types of drugs. The disadvantages are related to under-reporting, to missing information in the reports and to the lack of denominator data such as the user population and drug exposure patterns. Under-reporting is the biggest problem, but it is difficult to estimate precisely (Moride et al., 1997). This issue does not only apply to new drugs or

non-serious ADRs, but also to new drugs and serious ADRs. A systematic review of 37 different studies conducted in 12 different countries attempted to estimate the extent of under-reporting. According to this review, across the considered studies, its rate ranges from 6 to 100%, with a median under-reporting rate of 94%. It is not possible to give an exact estimate of the under-reporting level but it is probable to be in excess of 90% (Hazzel and Shakir, 2006).

The reasons for the phenomenon are multiple and complex. In 1976 (subsequently amended in 1986 and extended in 1996), Inman WHW presented a list of seven attitudes related to the causes of under-reporting involving of British physicians (Inman, 1976; Inman and Weber, 1986; Inman, 1996; Rossi Varallo et al., 2014). These "seven deadly sins", as he called them, were:

1. complacency as believing that serious ADRs are well documented and only safe drug is released in the market;
2. fear of getting involved in legal process or investigations of prescribing costs by health departments;
3. guilt for having been responsible for the damage caused to the health of the patient;
4. being ambitious and wishing to collect and publish one's own data;
5. ignorance regarding how to make a report (e.g. believing that only unexpected and serious ADRs must be reported);
6. fear of appearing ridiculous and being unsure about whether to report suspicions of ADR (e.g. believing that it is only necessary to report if there one is certain that the damage to the patient's health was caused by the use of specific medication);
7. lethargy, that is lack of interest, lack of time or other excuses related to postponing a report.

A systematic review has selected 45 articles and highlighted two other causes of under-reporting (Lopez-Gonzalez et al., 2009):

- indifference (i.e. feeling that one case that an individual doctor might see would not contribute to medical knowledge in general);
- feeling unsure (it is often nearly impossible to determine whether or not a drug is in fact responsible for a particular adverse reaction).

Understanding the causes that lead to non-compliance with the pharmacovigilance service is important so that further strategies can be developed to encourage health professionals to report ADRs thereby reducing this problem to a minimum. In this way, an efficacious action plan may be designed which takes into account the needs and aspirations of the people who report the cases, the resources available to implement the strategies necessary and the frequency with which they should applied. Continuing education, easy access to the registration form and its simplification are strategies that can be developed to increase the registration rates of ADR by health professionals (Rossi Varallo et al., 2014). New legislation would also help to solve the problem.

1.2.2 European pharmacovigilance legislation

There are differences between countries (and also between regions within countries) in the occurrence of ADRs and other drug-related problems. This may be due to many factors such as disease and prescribing practices, genetics, the diet and traditions of particular communities and the use and distribution of drugs (Mazzitello et al., 2013; Waller, 2010). The data resulting from a country may have greater relevance and educational value and may affect the national regulations of that country.

At European level, government agencies responsible for pharmacovigilance in Member States are in contact with each other and with the European Medicines Agency (EMA website). EMA has established a web-based European network (EudraVigilance) for the reporting and exchange of suspected ADRs during the pre-authorization phase and post-authorization phase of medicinal products in the European Economic Area. All pharmacovigilance activities are governed by rules that have changed over the years according to requirements.

European Pharmacovigilance legislation was changed in December 2010 and has been effective since July 2012 with the adoption of the EU Regulation 1235/2010 and Directive 2010/84/EU (Directive 2010/84/EU, 2010; EU Regulation 1235/2010, 2010). In Italy, this law became effective on 30 April 2015 with a Ministerial Decree published as n°143 in the Italian official gazette on 23 June 2015 (Italian Ministerial Decree, 2015).

This last directive amended the definition of adverse drug reaction in order to comprise noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from abuse, medication errors, misuse, occupational exposure, off-label use and overdose (Table 1) (Directive 2010/84/EU, 2010; EMA, 2012).

Table 1. Different use of drugs included in the last definition of adverse drug reaction.

Condition	Description
Abuse	The persistent or sporadic intentionally excessive use of a medicinal product accompanied by harmful physical or psychological effects
Medication errors	Any unintentional errors in the prescribing, dispensing or administration of a medicinal product while in the control of a healthcare professional, patient or consumer.
Misuse	Any situations where the medicinal product is intentionally and inappropriately used in a way which is not in accordance with the authorised product information.
Occupational Exposure	The exposure to a medicinal product as a result of one's professional or non-professional occupation.
Off-label use	Any situations where the medicinal product is intentionally used for a medical purpose which is not in accordance with the authorised product information.
Overdose	The administration of a quantity of a medicinal product, given per administration or cumulatively, which is above the maximum recommended dose according to the authorised product information. Clinical judgement should always be applied in this case.

Most of these situations represent an inappropriate use of drugs resulting in ADRs which could be avoided. Literature estimates that, worldwide, more than 50% of all medicines are prescribed, dispensed or sold inappropriately, while 50% of patients fail to take them correctly (WHO, 2002a).

An irrational use of medicines may actually increase the risk of preventable ADRs. Several studies have investigated the frequency of potentially preventable ADRs resulting in hospitalisation (Bates et al., 1995; McDonnel and Jacob, 2002; Pirmohamed et al., 2004), which a recent meta-analysis estimates ranging from 24 to 88% (Hakkarainen et al., 2012).

The EU Directive exhorted member States to operate changes in their pharmacovigilance systems in order to collect ADR reports according to the EMA definition. Some countries, such as Italy and Spain, have introduced a specific section on their ADR reporting form to indicate if the adverse reaction is related to abuse, medication errors or misuse etc.; others, such as the UK and France, have only prompted healthcare professionals to clarify this information in the narrative section of the form (Magro - Arzenton et al., 2016).

In particular, following the new European definition of ADR, in July 2012 the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) also modified its reporting form and to include a specific section ("Section 7") where the person reporting can specify whether the ADR has been caused by medication error, abuse/misuse, off-label use, overdose, occupational exposure or drug-drug interaction (DDI). The National Pharmacovigilance Network (NPN, Rete Nazionale di Farmacovigilanza) of Italy, the database that collects the ADR reports, was also changed. In this way, it is now possible to both collect the data and analyse them.

1.2.3 Italian pharmacovigilance system and database

In Italy pharmacovigilance started in the 1960s when physicians were required to report to the Ministry of Health any information regarding toxic effects and secondary consequences related to drug use. Over the years further legislation has been introduced to involve health care professionals in the control of drug safety (Mazzitello et al., 2013). With the introduction of the Law 531/87 in 1987, the

local health units became involved and people reporting were required to notify responsible for pharmacovigilance in the local health unit about the most serious cases and any deaths. The units then sent the reports to the Ministry of Health.

In 1997, the National System of Pharmacovigilance was established and in 2001 the National Pharmacovigilance Network was set up. As a result of subsequent legislation (with the last Ministerial decree coming into effect on 30 April, 2015), regulations were established regarding methods of reporting (i.e. by means of paper forms or online), who can report (i.e. all healthcare professionals and patients) and what they can report (i.e. all suspected adverse reactions - both serious and non-serious, both expected and unexpected – regarding the use of all drugs and vaccines) (Italian Ministerial Decree, 2006; Italian Ministerial Decree, 2015).

The Italian pharmacovigilance system is coordinated by the AIFA and consists of local structures which are responsible for pharmacovigilance, regional pharmacovigilance centres and Italian regional offices.

Anyone wishing to report is required to send their report of a suspected ADR by means of the appropriate form to the person responsible locally for pharmacovigilance in the local health unit. After verifying that the form has been fully completed and is consistent with requirements, this person then inserts the report into the NPN no later than seven days from receipt. The information that is inserted includes the role of the person reporting, the gender and age of the subject of the report, the nature of the adverse reaction and the degree of seriousness of the reaction, information regarding which drugs are suspected to have been the cause of the reaction and regarding any other concurrent therapy. It is possible to update the report at a later stage. The NPN does not only collect these spontaneous reports, but also extracts, manages and analyses the data (Figure 4).

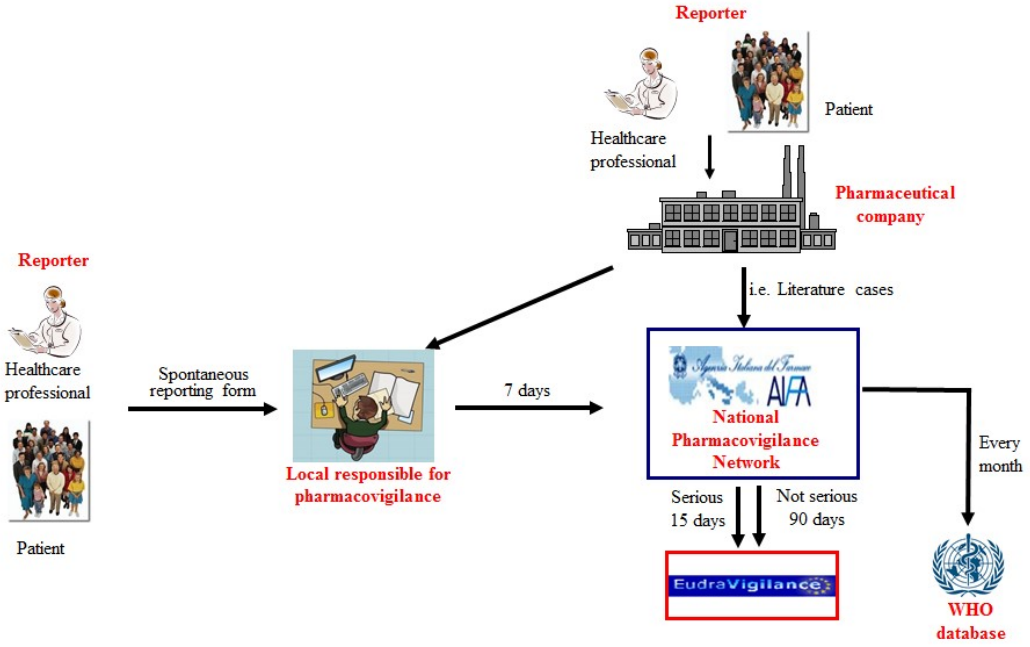

Figure 4. The Italian spontaneous reporting system

The pharmacovigilance system involves healthcare professionals and patients (who fill in the spontaneous reporting form), the pharmaceutical companies, the person responsible for pharmacovigilance and the national authority (AIFA). All reports are periodically transmitted to the European database (EudraVigilance) and WHO database (VigiBase).

Periodically these data are transmitted to the EudraVigilance database, the European database of suspected ADR reports managed by the European Medicine Agency, and to VigiBase, the WHO global database which includes ICSR coming from different countries worldwide.

1.2.4 VigiBase

VigiBase is a unique WHO global database of ICSRs (https://www.who-umc.org/vigibase/vigibase/). It is the largest database of its kind in the world, with over 14 million reports of suspected adverse drug reactions which have been received since 1968 from countries that are members of WHO Programme. As mentioned above, the WHO Programme for International Drug Monitoring

involves a group of more than 150 countries that share a vision concerning the safer and more effective use of medicines (Lindquist, 2008; Olsson, 1998). Since 1978, the Uppsala Monitoring Centre (UMC) in Sweden has been responsible for the technical and operational aspects of the Programme.

The database contains reports from both voluntary and regulatory sources and it is updated with incoming ICSRs on a continuous basis. Each member country is recommended to send reports on a regular basis, preferably more than once a month but at least every quarter. National Pharmacovigilance centres are given unrestricted access to all information in the VigiBase (WHO website). VigiBase is a computerised system in which data are recorded in a structured, hierarchical form to allow for easy and flexible retrieval and analysis. Each ICSRs contains details on the patient, such as age and sex, on type of ADR(s), on the drug(s) involved and any further information such as the country of origin and qualifications of the person reporting. For each drug, the database contains information on the duration and indication of use and dosage and whether the drug is suspected, interacting or concomitant. Some information (such as dosage and concomitant drugs) are frequently lacking. (Lindquist, 2008). VigiBase includes free text fields, for example, for patient disease and descriptions of the adverse reactions. However, most fields are linked to controlled vocabularies that contain predefined, allowed values, expressed as formatted text or codes. The suspected ADRs are coded using WHO-Adverse Reactions Terminology (WHO-ART) and the Medical Dictionary for Regulatory Activities (MedDRA) (Almenoff et al., 2005; MedDRA website). The drugs reported are classified according to the WHO Drug Dictionary which uses the hierarchical Anatomical Therapeutic Chemical (ATC) classification (Lindquist, 2008; MedDRA website). Both terminologies have a hierarchical organisation that allows data retrieval and analysis at different levels of specificity.

1.2.5 Medical Dictionary for Regulatory Activities

It is fundamental that the specific terminology is used in order for the data to be managed, analysed and codified in terms of the pharmaceuticals, pathologies and ADRs involved. The Medical Dictionary for Regulatory Activities lists

international medical terminology which has been developed under the auspices of the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. MedDRA was adopted for the first time in 1994. Prior to its development, the use of multiple terminologies raised several problems that complicated data retrieval and analysis and made it difficult to cross-reference data. Its regular maintenance and evolution is assigned to the MedDRA Maintenance and Support Services Organization (MSSO). (MedDRA website) It is updated twice a year in March and September with the most recent version being 19.1 of September 2016. Each term corresponds to a univocal code consisting of 8 numbers. These terms are organised in a hierarchical, multi-axial, associative structure (Figure 5).

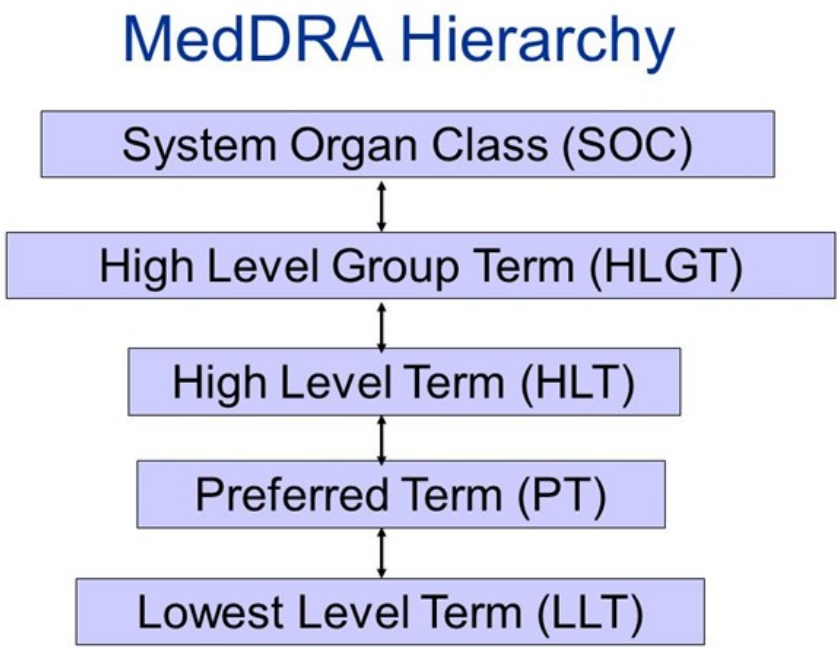

Figure 5. Structural hierarchy of MedDRA Terminology

The hierarchy is developed on five levels which represent vertical connections between the various terms (see Figure 5) with each level corresponding to a different degree of specificity. The levels of the structural hierarchy are as follows:

- Lowest Level Terms (LLTs) constitute the lowest level of the terminology. They can be “current” or “non-current”, synonyms or lexical variants. Each LLT is linked to only one Preferred Term
- Preferred Terms (PTs) represent a distinct and single medical concept. There is no limit to the number of LLTs that can be linked to a PT, however, a PT must have at least one LLT linked to it. PTs are subordinate to HLTs and they must be linked to at least one SOC.
- High Level Terms (HLTs) and High Level Group Terms (HLGTs) represent a grouping level and not a classification level. HLGTs are subordinate to System Organ Classes. An HLGT must be linked to at least one SOC and to at least one HLT.
- System Organ Class (SOC) is the highest level of the hierarchy. It provides the broadest concept for data retrieval. SOCs comprise groupings by aetiology, manifestation and purpose. A SOC is related directly to at least one HLGT and each PT is assigned a primary SOC.

The most recent version of the MedDRA consists of 76,000 LLTs and 27 SOCs.

1.2.6 Abuse potential and abuse liability relating to drugs

The amount of safety testing that is required for the registration of new drugs for human use has been steadily increasing over the last 20–30 years and this trend shows no signs of abating. An assessment of the potential for recreational abuse and/or liability to induce tolerance, physical dependence and a withdrawal (or discontinuation) syndrome is a mandatory part of testing that is required by the FDA (Food and Drugs Administration) and EMA (European Medicines Agency) for new chemical entities (NCE) that extensively cross the blood–brain barrier (irrespective of whether or not the brain is the primary site of therapeutic action) and act on central nervous system (CNS) (Calderon et al., 2015).

The term abuse potential refers to drugs that are used in non-medical situations, repeatedly or even sporadically, for the positive psychoactive effects they produce. These drugs are characterised by their central nervous system (CNS) activity. Examples of the psychoactive effects that may be produced include

sedation, euphoria, perceptual and other cognitive distortions, hallucinations and mood changes (FDA/CDER, 2017). Drugs with abuse potential often (but not always) produce psychic or physical dependence and may lead to addiction. Addiction is defined as a chronic, neurobiological disorder with genetic, psychosocial and environmental aspects, characterised by impaired control over drug use, compulsive use, continued use despite harm and craving (AAPM, 2001). From a regulatory and public health perspective, abuse liability refers not only to abuse potential, but also to all factors impacting the risk of misuse, abuse or diversion in the broader community (post-market) setting. Such factors include not only the intrinsic positive and reinforcing effects of a drug, but also its therapeutic indication, availability, ease of synthesis, context of use and risk for misuse or diversion. The potential for negative outcomes resulting from abuse (e.g. addiction, overdose or toxicity) is also included (Romach et al., 2014; Schoedel and Sellers, 2008).

The terms abuse potential and abuse liability have often been used interchangeably because they represent similar concepts. However, abuse liability encapsulates human social and environmental factors that reflect the consequences or liability of abuse which can be difficult to predict prior to marketing of a drug and difficult to recreate in a laboratory environment (Calderon et al., 2015).

An overview of the data required for an abuse liability evaluation by a regulatory authority prior to marketing approval is provided in Figure 6. The exact timing of the data collection will vary with the nature of the drug, as well as business decisions related to drug development.

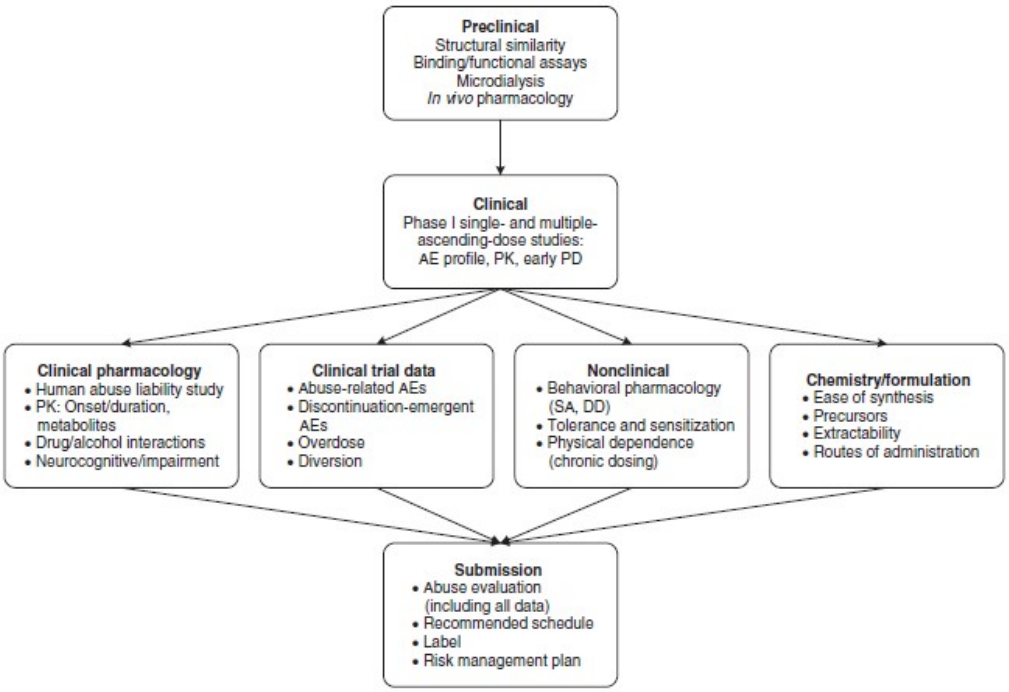

Figure 6. An overview of abuse liability data collection during drug development. The exact order and nature of any assessments carried out will depend on what is observed at previous stages and the developer's acceptable level of risk/control. AE, adverse event; DD, drug discrimination; PD, pharmacodynamics; PK, pharmacokinetics; SA, self-administration. Image taken from Schoedel and Sellers, 2008.

Preclinical and clinical behavioural studies may suggest which medication might be abused, but their methods have limited validity (Arfken and Cicero, 2003; Ator and Griffiths, 2003; Griffiths et al., 2003). Pre-marketing studies conducted to assess efficacy have limited potential to detect abuse due to the small and select samples participating in clinical trials and the type of protocols typically employed (Brady et al., 2003). As such, there is a need to both validate the results of behavioural studies and assess the actual abuse of specific medications in the general population at the earliest possible time following their introduction onto the market (Arfken and Cicero, 2003). Current Phase IV post-marketing data collection serves an important public health role even if this methodology has well known limitations (McColl and Sellers, 2006).

1.3 AIM

Clinical studies make it possible to evaluate the efficacy of a drug, but there are have some limitations regarding adverse drug reactions, especially about those that may arise after the drug has been used for a long time. Also in controlled studies that evaluate the effect of ketamine as an antidepressant, there are currently no data regarding the efficacy and safety of ketamine maintenance, considering that the longest duration of ketamine treatment has been only 6 weeks (Newport et al., 2016). Thus, as Newport and colleagues said, there is reason to be concerned regarding the potential perils of long-term ketamine administration. Furthermore, it should be taken into account that in November, 2015, WHO's Expert Committee on Drug Dependence (ECDD) reviewed ketamine among drugs "with potential for dependence, abuse and harm to health". This was to make recommendations to the UN Commission on Narcotic Drugs (CND) on the need for their international control (Taylor et al., 2016). The ECDD recommended unequivocally that ketamine should not be placed under international control as they concluded that ketamine abuse does not pose a global public health threat and that such control would limit access for those who most need it as a life-saving anaesthetic (WHO, 2015).

In particular, five main issues were addressed. These concerned whether:

1. clinical studies give sufficient safety information regarding the antidepressant use of ketamine;
2. pharmacovigilance provides information about the differing safety profile of ketamine when it is used as anaesthetic as compared to when it is used as an antidepressant;
3. the new ADR definition facilitates the detection of ketamine abuse;
4. the excessive control of a drug is necessary if it is already aware that this drug is safe, useful and economic
5. pharmacovigilance activities related to spontaneous reporting system can be a helpful instrument for the abuse liability assessment.

To answer these questions, the following analyses were performed on:

- clinical trials regarding the antidepressant use of ketamine in terms of their safety profile;
- the reports in the WHO database in order to compare the safety profile of ketamine when it is used at sub-anaesthetic or anaesthetic doses;
- the database of the National Pharmacovigilance Network to assess the impact of the new pharmacovigilance law after its introduction;
- the WHO database to detect the reports referring to ketamine abuse.

2. THE ANTIDEPRESSANT EFFECTS OF KETAMINE: FROM CLINICAL TRIALS TO POST-MARKETING SURVEILLANCE

2.1 AN OVERVIEW OF CLINICAL TRIALS

2.1.1 Introduction

Clinical trials are studies that make it possible to evaluate the efficacy and safety of medications or medical devices by monitoring their effects on groups of people and by measuring certain outcomes in the participants of these trials. The participants are assigned to receive one or more interventions (or no intervention) and these assignments follow a pre-defined plan or study protocol. They are conducted only after health authority/ethics committee approval has been received. Clinical trials may also compare a new medical approach for a specific health condition to a standard one that is already available, to a placebo that contains no active ingredients or to no intervention. Currently, clinical trials are designed as randomised, double-blind and placebo-controlled:

- randomized: each study subject is randomly assigned to receive either the study treatment or a placebo;
- blind: the subjects involved in the study do not know which study treatment they receive. If the study is double-blind, the researchers also do not know which treatment a subject receives;
- placebo-controlled: the use of a placebo (fake treatment) allows the researchers to isolate the effect of the study treatment from the placebo effect.

Although the term "clinical trial" is most commonly associated with large studies that involve many people, many clinical trials are small.

Sometimes, a meta-analysis and/or systematic review are conducted to obtain an overview of a specific topic. A systematic review answers a defined research question by collecting and summarising all empirical evidence that fits pre-specified eligibility criteria while a meta-analysis, which is a subset of a systematic review, is a statistical procedure to integrate the results of several independent studies.

During recent years, many clinical studies have been performed to assess the efficacy of ketamine as an anti-depressant and in order to obtain an overview of its tolerability, an analysis of these studies was conducted by means of a systematic review or meta-analysis of safety data.

2.1.2 Method

Search strategy

In order to perform a systematic review and/or meta-analysis regarding the safety of ketamine as an anti-depressive the studies were researched in various different computerized databases: PubMed (Medline database), Embase, PsycINFO, BIOSIS, Science Direct and the Cochrane Central Register of Controlled Trials until July 2014. The search strategy was based on the combination of terms "ketamine" as well as indexed terms related to depression ("Depression" OR "Depressive Disorders" OR "Mood Disorders" OR "Affective Disorders," OR "Anxiety") and study design ("controlled clinical trial").

Criteria for selecting articles

Studies were included if they satisfied all of the following criteria:

- Design: randomised controlled trials (RCT) with clinical remission and response to the treatment.
- Treatment characteristics: ketamine administration (one administration or more, alone or with another anaesthetic agent). Electroconvulsive therapy (ECT) studies and non-ECT studies were included.
- Subjects: participants with a diagnosis of major depression (unipolar or bipolar, resistant or not) assessed on a validated scale.

Data synthesis and analyses

The titles and abstracts on database records were screened and full texts retrieved for eligibility assessment. With the help of an expert in this sector, data were

extracted in a standard electronic form with: author name, date of publication, design, sample size, number of MDD included subjects, depression assessment scales, delay to depression assessment, diagnoses of resistant depression in inclusion criteria, co-administration of ECT sessions, previous withdrawal of antidepressant medications ("drug-free studies"), administered treatment of the cases and the control groups, and the ketamine dose administered. Firstly, the markers of internal validity from the Cochrane risk of bias tool were used (Higgins et al., 2011). Secondly, the studies were classified according to the level of evidence they provided using the classification scheme requirements for therapeutic questions (Gross and Johnston, 2009). The was done using a four-tiered system (class I to class IV), with class I indicating the strongest evidence and class IV the weakest. Finally, any sections in the studies relating to ADRs were taken into account and under the supervision of one of the leading experts in the field of systematic reviews and meta-analysis, it was determined whether there were the criteria to apply a systematic review or a meta-analysis of the safety aspects concerning the use of ketamine.

2.1.3 Results

The selection process is detailed in Figure 7. Fifty-five abstracts were initially identified by means of database searches; 41 articles were excluded because they did not meet the inclusion criteria and ten non-ECT studies and four ECT studies were included in analysis (Abdallah et al., 2012; Berman et al., 2000; Diazgranados et al., 2010a; Ghasemi et al., 2014; Jarventausta et al., 2013; Kudoh et al., 2002; Lapidus et al., 2014; Loo et al., 2012; Murrough et al., 2013; Sos et al., 2013; Valentine et al., 2011; Wang et al., 2012; Zarate et al., 2006; Zarate et al., 2012).

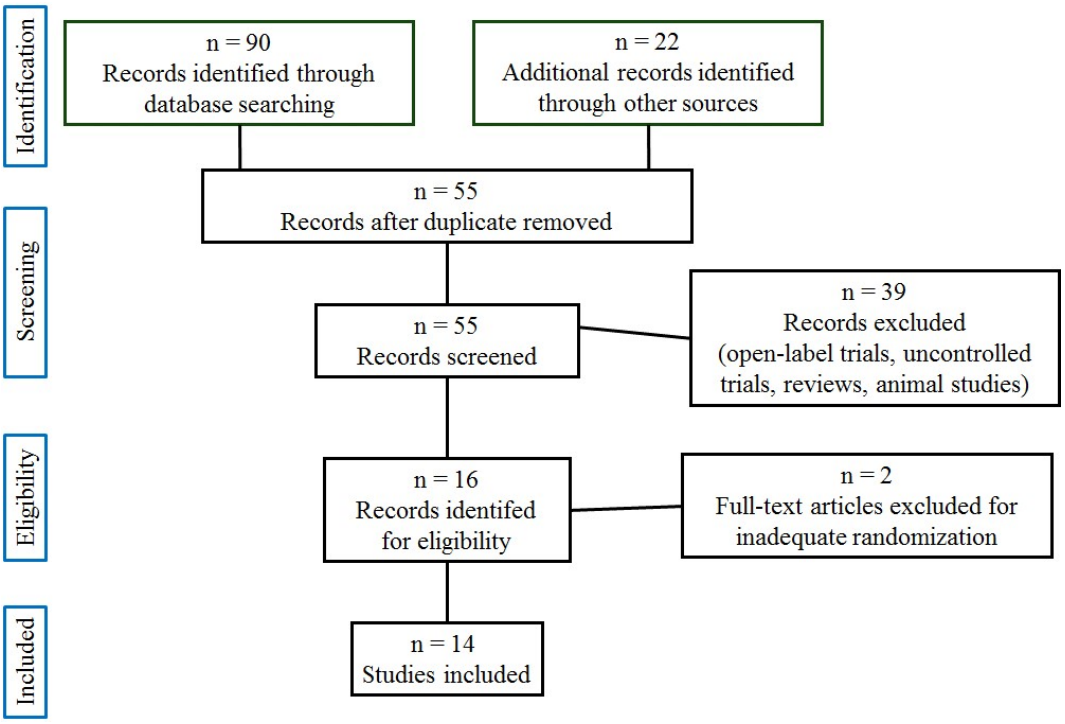

Figure. 7. Study selection flowchart

Unfortunately, the ADRs were described and reported in different ways in the studies (Table 2). Sometimes there was a specific ADR table, but in most cases the ADRs are reported in the main text without a specific analysis. Usually the exact number of patients who experienced an ADR was not reported. Furthermore, in the methods section of these studies, the terminology used to identify ADRs was not indicated. For these reasons, it was impossible to carry out a systematic review or meta-analysis.

Table 2. Studies considered and adverse drug reactions reporting method

Study	Adverse drug reactions (ADRs) reporting method
Abdallah et al. 2012	ADRs are reported, but the number of subjects involved is missing
Berman et al. 2000	There is no reference to the fact that ADRs have occurred
Diazgranados et al. 2010a	There is one paragraph in the text and a table showing ADRs and the number of subjects involved
Ghasemi et al. 2014	Some reactions are reported in the text, but without any indication of the number of subjects involved
Jarventausta et al. 2013	Some events are reported in the text, but these are not specifically referred to as ADRs
Kudoh et al. 2002	Some events are reported in the text, but these are not specified as ADRs
Lapidus et al. 2014	There is one paragraph in the text and a table showing ADRs and the number of subjects involved
Loo et al. 2012	Only any psychomimetic effects are considered
Murrough et al. 2013	There is a table specifying the ADRs found and the number of subjects involved
Sos et al. 2013	Some reactions are reported in the text, but without the number of subjects involved
Valentine et al. 2011	Some conditions are reported in the text, but these are not identified as ADRs and the number of subjects involved is not reported
Wang et al. 2012	Some reactions are reported in the text, but without any indication of the number of subjects involved
Zarate et al. 2006	ADRs reported in the text, but without the number of subjects involved
Zarate et al. 2012	ADRs are reported in the text along with a supplementary table with a list of ADRs and the number of subjects involved

2.2 AN ANALYSIS OF THE WHO DATABASE

2.2.1 Introduction

Recent research has shown that ketamine can induce long-lasting therapeutic effects on mood after a single low dose administration. Clinical studies have demonstrated that a single infusion of ketamine induces a rapid antidepressant response that lasts for up to 7 days in subjects with Major Depression Disorder (MDD) (aan het Rot et al., 2010; Berman et al., 2000; Diazgranados et al., 2010a, 2010b; Ibrahim et al., 2011; Machado-Vieira et al., 2012; Price et al., 2009; Zarate et al., 2006). During clinical trials of compounds that have yet to be commercialised, the therapeutic efficacy of a drug is evaluated and, if possible, compared to those of existing therapies. In addition, information about adverse reactions that may occur is gathered. In the case of ketamine, which has already been on the market for many years as an anaesthetic, safety information can also be found in spontaneous reports in the WHO database. ADR reports regarding off-label ketamine use as an antidepressant may also be present.

For this purpose, an extended analysis of the ICSRs contained in VigiBase was performed. The ADR reports in which the ketamine dose was specified were selected; in particular, the safety profile of two different dose groups (greater than or less than 30 mg) were analysed and compared. The 30 mg dose was considered to be a discriminative criterion between antidepressant (≤30 mg) and anaesthetic (>30 mg) uses of ketamine.

The aim was to provide a detailed description of the patterns of potential ketamine-like ADRs with the expectation that the pattern associated with the lower than 30 mg dose group could be used as a reference for ketamine-like antidepressant profiling.

2.2.2 Methods

Data source and study design

In order to evaluate the safety profile of ketamine, the reports of suspected ADRs in the WHO Global ICSRs Pharmacovigilance database (VigiBase) were examined. The analysis was performed using an old search and analysis tool for VigiBase known as VigiSearch.

VigiSearch, was a web-based program that included an interface for user defined database queries and standard preformatted outputs, ranging from summary listings such as the number of ICSRs by year, country, reaction or drug (in various combinations) to individual ICSRs. National Pharmacovigilance centres and regional centres had full access to the contents of VigiBase by means of a password for the VigiSearch web program (Lindquist, 2008).

This study was based on all the reports contained in VigiBase up to and including December 31st 2013. All the reports in which ketamine was the suspected drug were selected and, to exclude paediatric ADRs, the cases in which the age of the patients was >12 years old were analysed. In order to analyse the ADRs according to MedDRA terminology, the data were classified as SOC (the first level of MedDRA terminology) and PT (fourth level). Only reports containing information about age and dose were selected and then classified into 2 groups: ketamine dose ≤ 30 mg (Group A) and ketamine dose > 30 mg (Group B). The rationale for this cut-off was that ketamine at a dose ≤ 30 mg is usually used as an anti-depressant.

The reports were analysed by: gender, age, country of origin, reporter qualification, indication of use, administration route, other suspected and concomitant drugs and the type of adverse reaction. Means, percentages, and their 95% confidence intervals (95% CI) were used to compare the characteristics of patients and ADRs in the two different groups (A and B).

2.2.3 Results

On 31st December 2013, VigiBase contained 8,542,617 ICSRs of which 1,487 were related to ketamine use. 902 reports were selected according to the criteria. The analysis was performed on a dataset of 485 ICSRs, for which information on the ketamine dose was provided. Group A (ketamine dose ≤ 30 mg) included 104 reports (21%) and Group B (ketamine dose > 30 mg) 381 reports (79%). The analysis comprised reports from 46 countries with most of the reports coming from Australia, followed by the UK, Thailand and the USA (Figure 8).

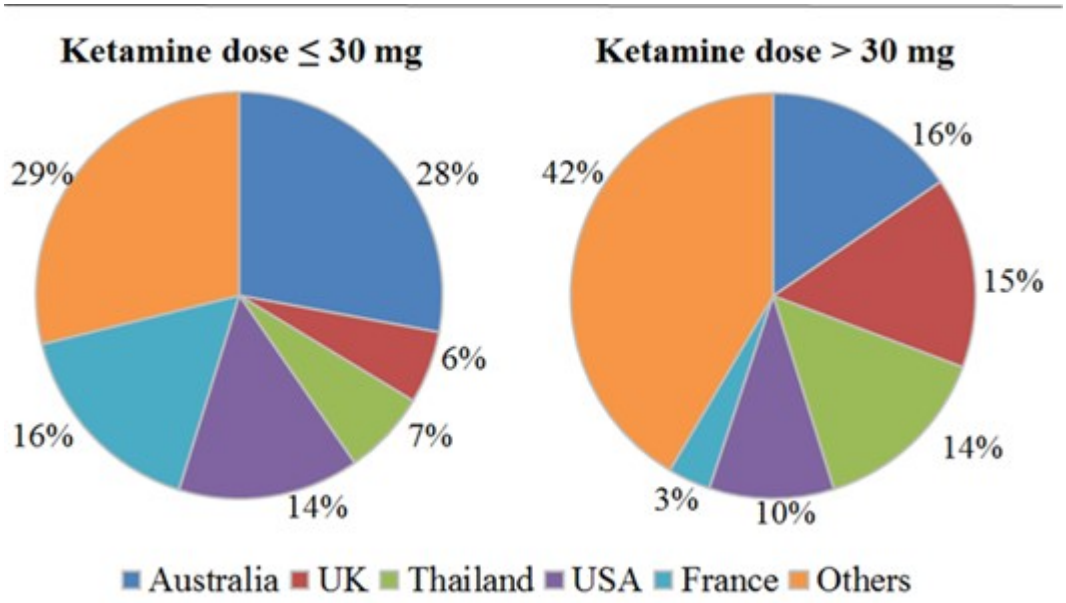

Figure 8. Percentage of ADR reports relating to ketamine by country. Only countries with a total of at least 6% are shown.

Interestingly, when taking into consideration the origin of the reports, the contribution of the USA to the dataset on ketamine (14% and 10% of the low and high dose reports respectively) is lower than the total number of reports from the USA in VigiBase. In fact, in general around 50% of all reports in VigiBase are from the USA.

Table 3 shows the main information for ketamine ADR reports. The sample populations of the two groups were almost equivalent: reports on females were slightly more than those on males and the average age was similar. A difference between the two groups was found regarding the suspected drugs. As a matter of fact, in Group A, in 51 cases ketamine was the only drug reported as suspected and in 22 of these cases there were no concomitant drugs, whereas in Group B there were 283 reports with ketamine was the only suspected drug and in 136 of these cases there were no other concomitant drugs. In the remaining cases, there were other suspected drugs. Physicians and pharmacists were the main source of the reports.

Table 3. The main information for ketamine reports divided into Group A (ketamine dose ≤ 30 mg) and Group B (ketamine dose > 30 mg)

	Group A (n=104)	**Group B (n=381)**
Gender, % (95% CI)		
Male	36.5 (27.2-45.8)	37.5 (32.6-42.4)
Female	61.5 (52.1-70.9)	60.6 (55.7-65.5)
Unknown	1.9 (-0.7-4.9)	1.8 (0.5-3.1)
Age (years), mean (95% CI)		
Male	42.1 (36.1-48.2)	43.0 (39.7-46.4)
Female	45.7 (40.9-50.4)	38.6 (36.0-41.1)
Unknown	41.0 (23.4-58.6)	42.1 (23.2-61.1)
Source of reports, % (95% CI)		
Physician	67.3 (58.3-76.3)	75.3 (71.0-79.6)
Pharmacist	6.7 (1.9-11.5)	6.6 (4.1-9.1)
Other Health Professionals	4.8 (0.7-8.9)	3.4 (1.6-5.2)
Others	15.4 (8.5-22.3)	8.7 (5.8-11.5)
Unknown	5.8 (1.3-10.3)	6.0 (3.6-8.4)
Suspected drugs, % (95% CI)		
Ketamine and other drugs	51.0 (41.4-60.6)	25.7 (21.3-30.1)
Ketamine		
Alone	21.1 (13.3-29.0)	35.7 (30.9-40.5)
With concomitant drugs	27.9 (19.3-36.5)	38.6 (33.7-43.5)

Unfortunately, an indication of use was not reported in most cases (about 69% in both groups).

Where it was reported, the use of ketamine for anaesthesia/surgery was higher in Group B than in Group A (Table 4). Consequently, the intravenous route was more frequent in reports with a ketamine dose > 30mg than in those with dose ≤ 30 mg.

Table 4. Administration route and indications regarding the type of use relating to ketamine. GroupA, ketamine dose ≤ 30 mg; Group B, ketamine dose >30 mg.

	Group A (n=104)	**Group B (n=381)**
Administration route, % (95% CI)		
Intravenous	66.3 (57.2-75.4)	74.5 (70.1-78.9)
Subcutaneous	5.8 (1.3-10.3)	3.7 (1.8-5.6)
Oral	2.9 (-0.3-6.1)	4.2 (2.2-6.2)
Intramuscular	2.9 (-0.3-6.1)	3.7 (1.8-5.6)
Others	3.8 (0.1-7.5)	3.9 (2.0-5.8)
Unknown	18.3 (10.9-25.7)	10.0 (7.0-13.0)
Indication, % (95% CI)		
Anaesthesia and surgery	9.6 (3.9-15.3)	16.3 (12.6-20.0)
Pain	9.6 (3.9-15.3)	7.9 (5.2-10.6)
Others	11.5 (5.4-17.6)	6.8 (4.3-9.3)
Unknown	69.2 (60.3-78.1)	69.0 (64.4-73.6)

In Figure 9, the ADRs in the ICSRs are summarized according to the SOC in MedDRA terminology. The ADRs in Group A corresponded to 14 SOCs whereas in Group B the ADRs corresponded to 20 SOCs. On the basis of a 95% CI (data not shown), no differences were observed between the groups. In both groups, most of ADRs were reported for the "Psychiatric disorders" SOC (27% of total ADRs in A and 21% in B), followed by "Nervous system disorders" (15% of total ADRs in A and 14% in B).

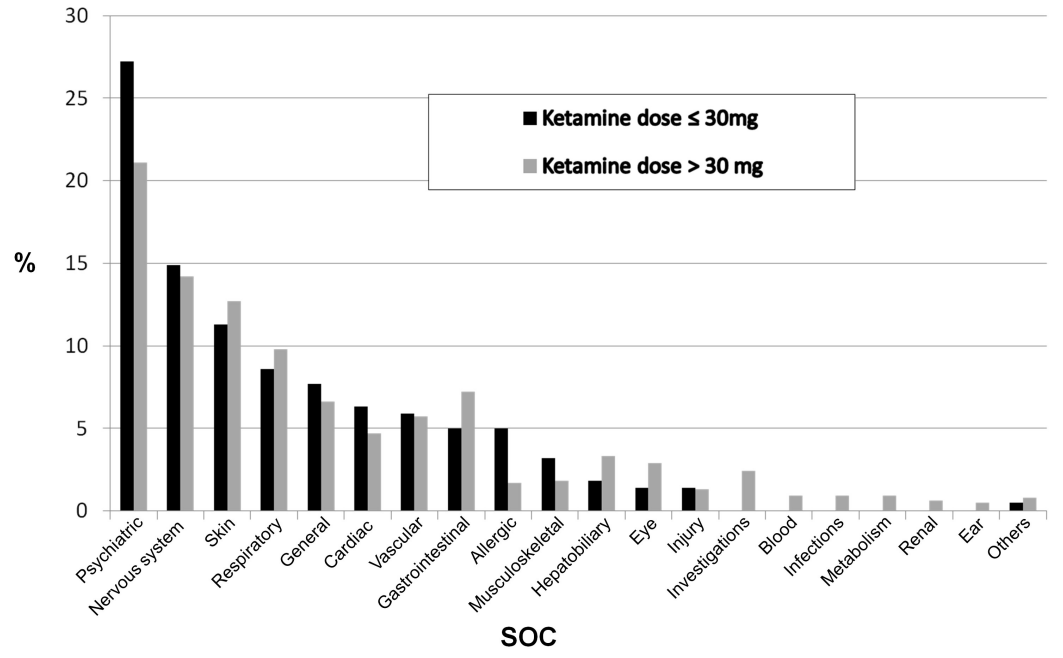

Figure 9. The type of ketamine adverse reaction, indicated as a percentage, grouped according to the System Organ Classes in MedDRA terminology.

In Table 5, the individual ADRs regarding Psychiatric and Nervous system disorders are listed. Among these, hallucination was the most frequently recorded type of ADR, with 20 of the total number of ADRs in group A (9.0%) and 45 in group B (5.7%). Some differences between the groups were observed in the cases

regarding Nervous system disorders. In fact, the most frequent ADRs in Group A were stupor, followed by convulsions and sedation/somnolence whereas in Group B, movement disorders (such as hypertonia, hyperkinesia and abnormal coordination, etc.) were more abundant, followed by convulsion and dizziness.

Table 5. Psychiatric and nervous reactions in Group A (ketamine dose ≤ 30 mg) and Group B (ketamine dose > 30 mg). The data are expressed as percentages of the total number of reactions, in brackets the 95% CI.

	Group A (n=221)*	**Group B (n=787)***
Psychiatric disorders	**27.1** (21.2-33.0)	**21.1** (18.2-24.0)
Hallucination	9.0 (5.2-12.8)	5.7 (4.1-7.3)
Alteration in mood and personality	6.3 (3.1-9.5)	3.8 (2.5-5.1)
Agitation/aggression	4.1 (1.5-6.7)	3.9 (2.5-5.3)
Confusional state	2.3 (0.3-4.3)	2.5 (1.4-3.6)
Delirium	1.8 (0.0-3.6)	0.9 (0.2-1.6)
Panic	1.4 (-0.1-2.9)	0
Nightmare	0.9 (-0.3-2.1)	2.2 (1.2-3.2)
Anxiety	0.9 (-0.3-2.1)	1.3 (0.5-2.1)
Suicidal ideation/attempt	0.5 (-0.4-1.4)	0.3 (-0.1-0.7)
Drug dependence	0	0.5 (0.0-1.0)
Nervous system disorders	**14.9** (10.2-19.6)	**14.2** (11.8-16.6)
Stupor	3.2 (0.9-5.5)	0
Convulsion	2.7 (0.6-4.8)	1.9 (0.9-2.9)
Sedation/somnolence	2.7 (0.6-4.8)	1.5 (0.7-2.3)
Other movement disorders	1.8 (0.0-3.6)	3.4 (2.1-4.7)
Dizziness	1.4 (-0.1-2.9)	1.7 (0.8-2.6)
Dyskinesia/myoclonus	1.4 (-0.1-2.9)	1.4 (0.6-2.2)
Headache	0.5 (-0.4-1.4)	1.4 (0.6-2.2)
Coma	0.5 (-0.4-1.4)	0.9 (0.2-0.6)
Paraesthesia	0	0.6 (0.1-1.1)
Others	0.9 (-0.3-2.1)	1.4 (0.6-2.2)

*The total number of reactions is higher than the total number of reports due to the fact that in many cases more than one adverse reaction was reported.

To sum up, the sample populations of the two groups, Group A (ketamine dose ≤ 30 mg) and Group B (ketamine dose > 30 mg), were very similar in terms of gender, age and the source of the reports. In many cases the reason for the use of ketamine was not reported while in both groups the most frequently reported administration route was intravenous. Most of the ADRs in both groups were related to the "psychiatric disorders" SOC, followed by "nervous system disorders".

3. KETAMINE ABUSE LIABILITY FROM A PHARMACOVIGILANCE PERPSECTIVE

3.1 AN ANALYSIS OF THE ITALIAN PHARMACOVIGILANCE DATABASE

3.1.1 Introduction

The most recent definition of the term Adverse Drug Reaction, introduced with the new European law in July 2012, covers noxious and unintended effects resulting not only from the authorised use of a drug at normal doses, but also from uses outside the terms of the marketing authorisation, including overdose, misuse, abuse, medication errors and suspected adverse reactions associated with occupational exposure (Directive 2010/84/EU, 2010; EMA, 2012). The aim of this part of the thesis is to understand how this new ADR definition has influenced spontaneous reporting, with a focus on ketamine abuse.

3.1.2 Method

Data source and study design

The source of the data was the NPN in Italy, a database which contains more than 300,000 suspected ADR reports collected since its creation in 2001. Following the new European definition of ADR, the AIFA has modified the Italian reporting form and included a specific section (Section 7) that makes it possible to report, collect and then analyse the ADRs deriving from various and different uses of drugs. In the database, the drugs are classified according to the Anatomical

Therapeutic Chemical (ATC) Classification and ADRs, comorbidities, laboratory tests and therapeutic indications are codified according to the MedDRA terminology (MedDRA website).

The reports included in the NPN from 1st January 2013 to 31st December 2015 were considered (with the exclusion of those associated with vaccines and cases cited in literature) in order to examine the data in the 3 years following the introduction of "Section 7" in the new ADR form. All reports in which "Section 7" had been filled in for at least one drug were selected, with no exceptions for patient age, patient sex or other factors. In particular, the data relating to ketamine abuse was taken into account. All the reports in the NPN in which ketamine is the suspected drug were also evaluated.

The data were extracted from the NPN using VigiSegn and a Microsoft Access Tool (Microsoft Office 2007 – Service Pack).

VigiSegn is a Decision Support System for pharmacovigilance activities based on a Data Warehouse with restricted access to the AIFA and Italian Regional Centres for Pharmacovigilance. It is an AIFA product which was developed by the Information Technology Team of the Pharmacology Unit at the University of Verona. It is based on an open source business intelligence server called Pentaho. The VigiSegn system has an underlying database and OLAP technology which can be accessed only by means of a high number of queries, reports or dashboards. All these queries have been carefully designed to show a specific set of data and to perform many types of analysis (Golfarelli and Rizzi, 2010). Chi-square test with Yates correction ($\chi 2$ test) was used when appropriate.

3.1.3 Results

122,368 reports sent between 1st January 2013 and 31st December 2015 were extracted according to the selection criteria from the national database. In 6,826 of these (5.6 %), "Section 7" had been completed. The percentage of reports with "Section 7" completed did not change very much over the three years considered (Table 6).

Table 6. Adverse drug reaction reports with "Section7" completed or not completed in the National Pharmacovigilance Network database (years 2013 to 2015). The total number of reports is also reported.

	Year			
ADR reports	2013	2014	2015	Total
"Section 7" completed, N (%)	1,833 (4.9)	2,668 (6.2)	2,325 (5.6)	6,826 (5.6)
"Section 7" not completed, N (%)	35,435 (95.1)	40,664 (93.8)	39,443 (94.4)	115,542 (94.4)
Total reports in NPN database	37,268	43,332	41,768	122,368

*ADR reports with "Section 7" completed are related to: medication errors, abuse/misuse, off-label use, overdose, occupational exposure and drug−drug interactions.

Figure 10 shows the causes of the ADRs indicated in "Section 7". Abuse/misuse was the most representative category, whereas the percentage of reports relating to drug-drug interactions and medication errors were similar (22.2% vs 21.4%). The distribution of the six categories did not change over the 3 years considered (data not shown).

Only for medication errors it is possible to have additional information and this was provided in the majority of cases (1054, 72%). In particular, in 56% of cases the errors were due to dosage, mainly as a result of the prescription being misunderstood; in 38% of cases they were associated with the drug itself, mainly due to another product with similar packaging or a similar name being mistaken for it; in 5% of cases they were related to a mistaken administration route and in the remaining 1% of cases they were related to a drug being taken after it had expired (data not shown).

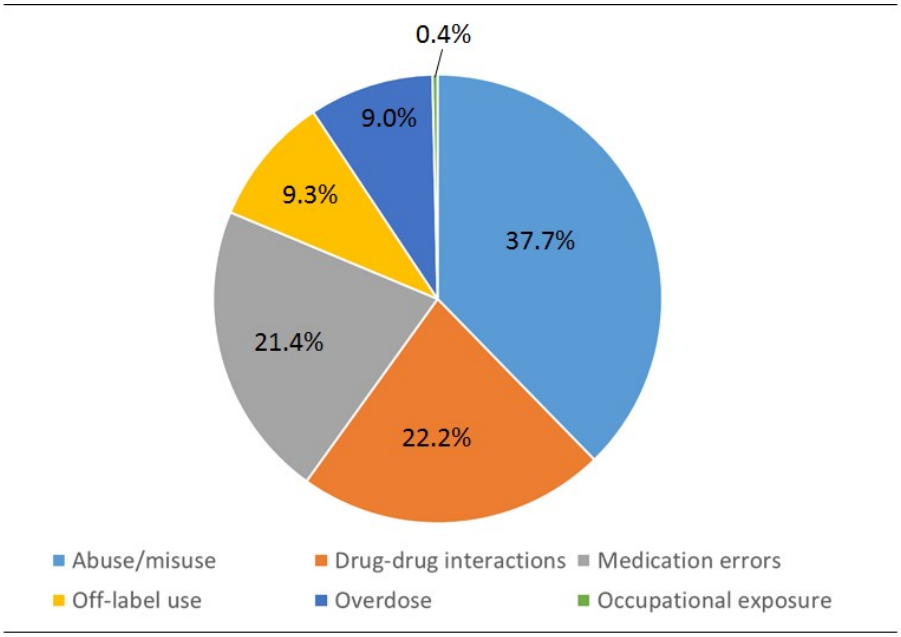

Figure 10. Adverse drug reaction reports with "Section7" completed divided into categories according to the cause. Data from the National Pharmacovigilance Network database (years 2013 to 2015). Categories are indicated as in the Italian ADR reporting form.

The percentage of cases with serious abuse/misuse reported in "Section 7" was extremely significant higher both with respect to other reports with "Section 7" completed (80.3 vs 57.0, $p<0.0001$) and with respect to the total number of reports presented to the National Pharmacovigilance Network over the study period (80.3% vs 35.1%, $p<0.0001$) (Table 7).

Most of the ADR reports came from physicians and the percentages were similar for all groups (e.g. 67.0% for abuse/misuse and 69.8% for all of the reports in the NPN). Among the reports originating from physicians, the number of reports from hospital physicians was greater in all groups (data not shown). With regard to pharmacists, the majority of the reports came from hospital pharmacists, who generally fill in the reports based on information received from clinicians.

Table 7. The seriousness and source of adverse drug reaction reports with "Section7" completed or not completed in the National Pharmacovigilance Network (NPN) database (years 2013 to 2015). The total number of reports in the NPN database is also reported.

	"Section 7" completed (%)		**"Section 7" not completed (%)**	**Total reports in NPN database (%)**
	Abuse/misuse	Other		
Seriousness				
Serious	2,067 (80.3)	2,424 (57.0)	38,504 (33.3)	42,995 (35.1)
Non-serious	501 (19.5)	1,765 (41.5)	73,507 (63.6)	75,773 (61.9)
Not available	6 (0.2)	63 (1.5)	3,531 (3.1)	3,600 (3.0)
Total	2,574 (100)	4,252 (100)	115,542 (100)	122,368 (100)
Source				
Physicians	1,725 (67.0)	2,709 (63.7)	80,929 (70.0)	85,363 (69.8)
Pharmacists	660 (25.6)	909 (21.4)	20,028 (17.3)	21,597 (17.6)
Drug Companies	61 (2.4)	103 (2.4)	2,766 (2.4)	2,930 (2.4)
Nurses	33 (1.3)	57 (1.3)	2,838 (2.5)	2,928 (2.4)
Patients	21 (0.8)	64 (1.5)	4,522 (3.9)	4,607 (3.8)
Other	74 (2.9)	410 (9.6)	4,459 (3.9)	4,943 (4.0)
Total	2,574 (100)	4,252 (100)	115,542 (100)	122,368 (100)

*Other categories are related to: medication errors, off-label use, overdose, occupational exposure, and drug −drug interactions.

Table 8 represents the ATC classes (third level) which were reported most frequently in cases of abuse/misuse. For each ATC class, the percentage refers to the total number of ATC classes relating to abuse/misuse (N=3,888). The most frequently reported drugs were anxiolytics (mainly benzodiazepines such as lorazepam, alprazolam and delorazepam), antipsychotics (mainly quetiapine) and anti-depressants (mainly paroxetine), with all classes acting on the Central Nervous System.

Table 8. The ATC classes (third level) in reports with "Section 7" completed for abuse/misuse. For each ATC class, the percentage refers to the total number of ATC classes relating to abuse/misuse. Data from the National Pharmacovigilance Network database (years 2013 - 2015).

ATC Class[a]	Abuse/misuse, N	Abuse/misuse, %
N05B- Anxiolytics	955	24.6
N05A-Antipsychotics	481	12.4
N06A-Antidepressants	452	11.6
N05C- Hypnotics and sedatives	404	10.4
N03A-Antiepileptics	385	9.9
M01A- anti-inflammatory and anti-rheumatic products, non-steroids	167	4.3
N02B- other analgesics and antipyretics	138	3.5

[a]Only the ATC classes with more than 100 reports are shown.

Up to and including 31st December 2015, there were 23 ADR reports in the NPN in which ketamine was indicated as the suspected drug. 21 of these referred to adverse reactions during the induction or maintenance of anaesthesia.
Of those reports in which "Section 7" was completed, ketamine was reported as a suspected drug in only one case which related to "abuse/misuse". This case was reported in 2015 and involved a patient who manifested anxiety, asthenia, dysaesthesia, dyspnoea and pre-syncope after inhaling ketamine and cocaine.
There was also another case in 2011 regarding the non-medical use of ketamine which had been taken by the subject in the form of an intramuscular injection together with delorazepam with the aim of self-injury. The resulting reactions included fever and myalgia.

To sum up, over the three years considered, "Section 7" had been completed in 5.6% of the total number of reports. With regard to the different categories of "Section 7", abuse/misuse was the most significantly representative category and the percentage of serious reports relating to this group was higher both with respect to other reports with "Section 7" completed and with respect to the total number of reports presented to the National Pharmacovigilance Network over the study period. The most frequently reported drugs relating to abuse/misuse were anxiolytics, antipsychotic and anti-depressant drugs. In the NPN there were 23 ADR reports in which ketamine was indicated as the suspected drug and only in one case was abuse/misuse indicated in "Section 7".

3.2 AN ANALYSIS OF THE WHO DATABASE

3.2.1 Introduction

As mentioned earlier, the WHO database collects ADR reports from all over the world (Lindquist, 2008; WHO website). Every country sends the information as they receive it in the form of a spontaneous report, the compilation and collection of which is registered in different ways by each country. For example, even though there is one set of regulations pertaining to pharmacovigilance in Europe, the reporting forms are not standard. Uniformity between the various countries

only regards the information that is required for the report to be considered valid, that is, at least one piece of information about the patient (either the sex, age or date of birth), information regarding the reaction and the suspected drug(s) and information regarding the reporter who must be identifiable and contactable.
This lack of homogeneity in terms of data collection in part comprises the analysis of the reports which is carried out on the WHO database (Lindquist, 2008). However, certain sections of the report forms are standardised and uniform, e.g. the age of the patient and information as to whether the pharmaceutical is suspected or concomitant. Furthermore, each report contains information regarding at least one drug, an ADR, the country submitting the report and an identification number. The difference between this database and the Italian database is that it is not possible to identify cases of abuse and misuse by means of consulting a specific section. The aim of this part of the thesis is to identify cases of improper use of ketamine from within the WHO database in order to understand to what extent an analysis of these reports can provide new information regarding its abuse/misuse and abuse liability.

3.2.2 Method

Data source and selection of cases

The WHO Global ICSR Database (VigiBase) contains more than 14 million ADR reports from 150 countries (Lindquist, 2008; Norén et al., 2007). As there is a possibility that some of the reports are duplicated, the removal of these duplicates is extremely important and it is fundamental that this is carried out by the UMC. The detection of duplicates within VigiBase is not just limited to a check of some elements and/or a manual verification of cases, but also includes specific statistical algorithms (Norén et al., 2007). As previously stated (see paragraph 1.2.4. VigiBase), the various different types of ADRs are coded according to the WHO Adverse Reactions Terminology (WHO-ART) and also the MedDRA terminology. The latter is made up of five levels of hierarchy (MedDRA website) and in this study the reports were extracted using the fourth MedDRA level which relates to preferred terms (PT). The drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system and are assigned a

rating depending on whether they are “suspected” (i.e. drugs suspected of being the cause of the ADR), “interacting” (i.e. it is suspected that the ADR is related to an interaction between two or more drugs) or “concomitant” (i.e. a drug which is used concurrently but is not suspected by the reporter to have caused the adverse event). The reports also contain additional information, such as the age and gender of the patient and the seriousness of the ADR which is classified according to ICH E2A criteria. Serious ADRs are divided into the following categories: fatal, life-threatening, requiring hospitalisation or prolongation of existing hospitalisation, resulting in persistent or significant disability/incapacity in the reporter's opinion or resulting in a congenital anomaly/birth defect or other serious medical conditions (Diamond et al., 2014). All other ADRs are classified as non-serious

For the purposes of this study, all ADR reports recorded until 31st December 2016 were taken into consideration, in particular those in which ketamine was reported as the suspected drug. Subsequently, in order to evaluate any improper use of ketamine, those reports in which at least one of the following preferred terms (PT) was reported were selected and analysed: behavioural addiction, completed suicide, dependence, drug abuse, drug abuser, drug dependence, drug diversion, drug withdrawal syndrome, intentional overdose, intentional product misuse, overdose, substance abuse, substance abuser, substance dependence, substance use, toxicity to various agents and withdrawal syndrome. The age and gender of the patients, the country of origin, the ADR in the reports extracted, concomitant drugs and indication of use were also considered.

3.2.3 Results

Taking into account the whole database, up to 31st December 2016, 14,040,453 ADR reports were inserted. In 2997 of these ketamine was the suspected drug. Of these, according to the PT listed above, 202 reports of ketamine abuse (6.7%) were extracted (Table 9).

Table 9. Main information regarding adverse drug reaction reports in the WHO database (up to 31st December 2016).

	Total reports in VigiBase	Reports with ketamine as suspected drug	Reports of ketamine abuse
Number	14,040,453	2,997	202
Country (%)			
Africa	0.9	1.4	0.0
Americas	54.0	27.2	49.5
Asia	17.9	23.2	0.5
Europe	24.2	41.8	49.5
Oceania	3.0	6.4	0.5
Gender (%)			
Female	56.6	48.2	29.7
Male	37.4	43.4	56.9
Unknown	6.0	8.3	13.4
Age (%)			
0 - 27 days	0.2	0.4	0.5
28 days to 23 months	2.7	3.8	3.5
2 - 11 years	3.7	20.8	3.5
12 - 17 years	2.4	7.0	3.5
18 - 44 years	20.3	25.8	58.4
45 - 64 years	24.4	19.9	7.4
65 - 74 years	11.5	5.9	0.5
≥ 75 years	9.4	4.1	0.5
Unknown	25.5	12.3	22.3

In the WHO database, most of the reports came from the Americas and of these, the majority come from the USA (6,787,396, 89.6%). As far as reports involving ketamine were concerned, however, the reports mainly originate from Europe (1,252, 41.8%), in particular from France (736, 58.8% with respect to the total number of reports from Europe) but an equal number of reports relating to the abuse of ketamine (N = 100) originate from the Americas (94% of these are from the USA) and Europe (34% from both France and the UK).

Table 9 also displays the distribution of reports according to age and sex. There were more females reported in the WHO database and in the reports involving ketamine (respectively 56.6% and 48.2%), while reports relating to ketamine abuse mainly involve males. With regard to age, 20.8% of the reports of ketamine use concerned the age range from 2-11 years, while more than half of the reports of ketamine abuse relate to the age range from 18-44 years (118, 58.4%).

In 2,997 of the reports in which ketamine was the suspected drug, information regarding the type of use was not provided in many cases (50%); the remaining cases mainly concern the use of ketamine for anaesthesia, analgesia and also for the management of pain (data not shown).

Focusing on the 202 reports relating to improper use, the distribution of the PTs is shown in Table 10.

Table 10. Statistics relating to the preferred terms used to select reports related to the abuse/misuse of ketamine from the WHO database (up to 31st December 2016).

Preferred Term	Number	Percentage
Drug abuse	74	36.6
Overdose	30	14.9
Drug dependence	27	13.4
Intentional product misuse	25	12.4
Toxicity to various agents	23	11.4
Withdrawal syndrome	16	7.9
Substance abuse	13	6.4
Intentional overdose	12	5.9
Completed suicide	11	5.4
Drug abuser	9	4.5
Drug withdrawal syndrome	8	4.0
Dependence	3	1.5
Drug diversion	3	1.5
Substance use	2	1.0
Substance abuser	1	0.5
Substance dependence	1	0.5

Table 11 shows the top twenty adverse reactions in these reports.

Table 11. Adverse drug reactions in reports of abuse/misuse of ketamine.

Adverse Drug Reaction	Number	Percentage
Coma	13	6.4
Biliary dilatation	11	5.4
Death	10	5.0
Cystitis	9	4.5
Hydronephrosis	8	4.0
Medication error	7	3.5
Drug interaction	6	3.0
Abdominal pain	5	2.5
Blood creatine phosphokinase increased	5	2.5
Confusional state	5	2.5
Cystitis ulcerative	5	2.5
Dyspnoea	5	2.5
Dysuria	5	2.5
Hypotension	5	2.5
Loss of consciousness	5	2.5
Malaise	5	2.5
Poisoning	5	2.5
Tachycardia	5	2.5

Grouping the ADRs reported according to HLT and SOC, it can be noted that the apparatus most commonly involved were nervous system disorders, psychiatric disorders and renal and urinary disorders.

Ketamine was the only suspected drug in 68 reports (34%), while the other most suspected drugs in remaining reports were cocaine (N=19, 9.4%), morphine (N=18, 8.9%) and clonidine (N=17, 8.4%). Death occurred in 59 cases (28%) and in only 5 of these cases was ketamine the only suspected drug.

To sum up, in the WHO database taken as a whole, ketamine was the suspected drug in 2997 ADR reports. 202 reports were extracted according to some preferred terms relating to abuse. In these latter, it is to be noted that there was a greater number of reports referring to male subjects aged between 18 and 44. Grouping the ADRs reported according to System Organ Class, it can be noted that the apparatus most commonly involved was nervous system disorders, followed by psychiatric disorders and renal and urinary disorders.

4. DISCUSSION

For the purposes of this project, ketamine was analysed in the context of its antidepressant use and abuse using an approach and instruments pertaining to pharmacovigilance. A critical analysis was then carried out on the information obtained regarding ketamine in order to determine the contribution pharmacovigilance might offer in the context of abuse liability.

In literature, there are many studies on ADRs relating to the use of ketamine as an anaesthetic (Reich and Silvay, 1989; Strayer and Nelson, 2008) and to its experimental use as an antidepressant (Diamond et al., 2014; Diazgranados et al., 2010a; Murrough et al., 2013; Zarate et al., 2006). Existing clinical trials indicate that the antidepressant effects of ketamine are as transient as they are rapid (Newport et al., 2016). Specifically, 1 week after ketamine infusion, the odds ratio for a remission of depressive symptoms is no longer statistically significant and the odds ratio for therapeutic response, though significant, falls from a peak of 24.7 to 4.6 (Newport et al., 2015). Existing data, therefore, indicate that the therapeutic response to ketamine lacks the durability of ECT treatment and thus ketamine infusion as an alternative to ECT for the acute treatment of depression is not indicated. However, there are currently no data regarding the efficacy and safety of ketamine as a maintenance therapy delivered intravenously, intranasally, or via other routes. In existing controlled studies, the longest duration of ketamine treatment was only 6 weeks (Singh et al., 2016) but there is reason to be concerned regarding the potential perils of long-term ketamine administration. For example, despite evidence supporting the neuroprotective benefits of ketamine, in some contexts ketamine may be neurotoxic. In particular, extended exposure has been posited as a risk factor for ketamine-induced neurotoxicity (Soriano, 2012). Systematic reviews and meta-analyses are a key element of evidence-based healthcare and these can provide additional global information regarding particular issues. While in the literature on the subject there are systematic reviews and meta-analyses which analyse the efficacy of ketamine as an anti-depressive (Caddy et al., 2014; Fond et al., 2014; Kishimoto et al., 2016; McGirr et al., 2015), to our knowledge, there are no publications which concern the application of these methods for the analysis of the adverse reactions which may

occur after a single or repeated doses of ketamine. More importantly, there are no systematic data regarding the safety related to long-term ketamine administration.
The choice was made to select those studies which concern the efficacy of treatment with ketamine as an anti-depressive and then assess the safety aspects mentioned in these publications. The articles selected were approved by an expert in the sector and the PRISMA guidelines were followed (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (PRISMA website). According to the indications provided by the expert, those studies demonstrating the efficacy of treatment with ketamine were extracted. Fond et al. had also published a systematic revision based on some of these (Fond et al., 2014).
As shown in Table 2, it was not possible by means of a preliminary analysis of the 14 studies which had been selected to carry out a systematic revision and/or meta-analysis of the safety aspects of the use of ketamine as an anti-depressive. Adverse reactions were either not even mentioned (Berman et al., 2000; Jarventausta et al., 2013; Kudoh et al., 2002; Valentine et al., 2011; Wang et al., 2012) or were reported in an unstructured fashion, often without any precise indication of the number of cases found (Abdallah et al., 2012; Diazgranados et al., 2010a; Ghasemi et al., 2014; Lapidus et al., 2014; Loo et al., 2012; Murrough et al., 2013; Sos et al., 2013; Zarate et al., 2006; Zarate et al., 2012). Some of the adverse reactions reported more frequently, such as nausea, dizziness and headache, were in line with the known safety profile of ketamine.
However, an analysis of the safety profile of ketamine was performed based on the WHO Global ICSRs database. To our knowledge this type of analysis had never been conducted before. The safety profile of ketamine was analysed according to two different categories: ketamine doses ≤ 30 mg (Group A) and ketamine doses > 30 mg (Group B), since 30 mg is considered to be the discriminating dose between its potential antidepressant use and its therapeutic anaesthetic use. Currently ketamine is used at low doses for cancer pain, maintenance of anaesthesia in continuous infusion and recreational purposes and it is under testing as an anti-depressant (Morgan and Curran, 2011).
The countries which contributed most frequently to VigiBase in this study had been members of the WHO drug monitoring programme for a considerable length

of time, i.e. the USA, the UK and Australia since 1968 and Thailand, which was the first Asian country to join in 1984 (Aagaard et al.,. 2012). The length of membership is probably correlated to the higher number of reports from these countries.

The main information in these reports concerns the fact that those involving women prevail (around 60%). This is in line with the characteristics of VigiBase, as shown in a study on gender distribution which confirmed that for the majority of reporting countries, SOCs and ATC groups since 1968, when WHO drug monitoring programme started (Friden et al., 2009), the reports predominantly concern females. Many studies have suggested that women are more at risk factor for ADRs and this appears to be related to gender-based physiological characteristics as well as differences in pharmacodynamics and pharmacokinetics (Rademaker, 2001; Tran et al., 1998; Zopf et al. 2008). The dominance of reports concerning females is, however, balanced between the two groups in our study. The mean age of the patients (approximately 40 years) did not vary much with respect to gender and Group. Group B featured a higher number of ADR cases, probably because the controlled use of ketamine as an anaesthetic is prevalent and therefore proportionally more frequently reported. When analysing the drugs indicated in the reports, in Group A ketamine was not the only suspected drug in many cases. Thus, there is a difference between Groups A and B concerning the data related to the suspected drug (reported as “ketamine alone” and “ketamine and other drugs”). On the other hand, it should be borne in mind that in most reports the concomitant use of other drugs was often omitted and as a result this difference is of limited significance. The administration route was indicated in many reports and in both groups the most frequent administration route was intravenous. Unfortunately, an indication of the type of use was reported in only about 30% of the cases.

The ADR types, grouped according SOCs, were comparable and there were no apparent differences between the safety features of the two groups. Approximately most of ADRs occurred with the same probability in the two groups; the greater number of SOCs in the high dose group (ketamine dose > 30 mg) may be due to the larger sample size since this is the therapeutic dose normally used. In

"psychiatric disorders" and "nervous system disorders" SOCs (the main SOCs for both groups), the most commonly occurring ADRs were hallucination, alteration in mood and personality, agitation/aggression, confusional state, delirium, convulsion, sedation/somnolence and other movement disorders. These ADRs have been listed in many studies addressing the benefits and limitations of ketamine in analgesia and anaesthesia (Reich and Silvay, 1989; Strayer and Nelson, 2008) and in other studies regarding the safety and tolerability of ketamine as an anti-depressant in clinical trials (Diamond et al., 2014; Diazgranados et al., 2010a; Murrough et al., 2013; Zarate et al., 2006).

The aim of this part of the thesis is to demonstrate that analysing a spontaneous reporting database is a useful approach in order to study the safety profile of a drug and add to information originating from data on ADRs related to the therapeutic or experimental use of ketamine. The findings show that the drug is characterised by good tolerability at either dose which suggests that the pattern of the ADRs relating to ketamine does not depend on the dosage. It is also interesting to note that the anticipated concerns regarding the "non – Psychiatric and Nervous system disorders" SOCs are lower than expected and in part appear to be dose-related. Clinicians should be aware that Psychiatric and Nervous ADRs might occur even at low doses.

The other issue which has been addressed in this study regards the data relating to the abuse of ketamine. An analysis was carried out on both the Italian database and in the WHO database.

The most recent European pharmacovigilance legislation, which amended the definition of ADR, emphasised that it is possible to report adverse drug events not only related to the authorised use of drugs at normal doses, but also in cases of medication error, abuse, misuse or overdose, all of which are closely related to inappropriate use. To our knowledge, few European Countries (i.e. only Italy and Spain) modified the ADR reporting form after the new legislation by adding specific fields in order to improve the possibility of identifying the causes of adverse events. In other countries, the reporter is invited to describe these types of ADRs in the narrative section. "Section 7" is specific and structured in the Italian form and this facilitates an analysis of the ADR reports linked to inappropriate use

and provides better quality of information as compared to reports which are less structured or even lack similar fields (Magro - Arzenton et al., 2016). Therefore, in the light of all the issues mentioned above, while data show that the percentage of ADR reports relating to inappropriate use constitute only a small part of the Italian database (5.6%), these cases were in fact consistently reported during the three years considered in the study. The category relating to abuse/misuse was predominant among those reports citing inappropriate use, followed by drug-drug interactions and medication errors. The percentage of serious reports was higher for those with "Section 7" completed as compared to serious reports in the NPN database. In fact, this is not unexpected since all of the situations reported in "Section 7" are, according to literature, related to more serious events (Laroche et al., 2007). Most came from hospital physicians and pharmacists and this is in line with national data regarding the same issue (Italian Medicines Agency - AIFA website, 2013). Despite the fact that in the NPN database the terms abuse and misuse are reported together, it is possible to differentiate between them by means of an analysis of the drugs involved. Predictably, anxiolytics in particular, mainly benzodiazepines (BDZ), are frequently linked to abuse and antipsychotic (mainly quetiapine) and anti-depressant drugs (mainly paroxetine) to misuse/abuse. The issue of BDZ abuse is widely described in literature (Chen et al., 2011; Horyniak et al., 2012). The consumption of BDZs is often chronic and many people take these drugs for many years (Egan et al., 2000; Neutel 2005), despite guidelines recommending their use to be limited to a few weeks. As a matter of fact, this incorrect use causes dependence with the onset of tolerance (Vinkers and Olivier, 2012), the rising health costs associated with this problem fall (Berger et al., 2012) and, according to some authors, there is also an increased risk of dementia (Billioti de Gage et al., 2012). In the literature on the subject, quetiapine, an atypical antipsychotic, is the subject of a series of case reports that suggest its potential misuse/abuse. The pharmacological theories to explain risk remain unsubstantiated, and there are no available animal or human empirical studies to clarify the potential risk (Sansone and Sansone, 2010). Although anti-depressants are generally thought to be associated with a low abuse tendency, there is evidence in the literature of their misuse, abuse, and dependence. Most reported

cases of anti-depressant abuse occur in individuals with comorbid substance use and mood disorders. The most common motivation for abuse, in all classes of anti-depressants, is to achieve a psychostimulant-like effect, including a desire for a "high" or euphoria (Evans and Sullivan, 2014).

Instead, with regard to reports involving ketamine in the Italian database, the results were unfortunately disappointing. As mentioned in the results section, ketamine was reported as a suspect drug in only 23 cases. These cases were distributed relatively evenly across the period of time investigated except for a peak in 2009 with 9 reports all concerning the use of ketamine as an anaesthetic. The new 2012 definition of ADR, which made it possible to report cases of abuse and the relative adverse reactions, did not have any effect on reports relating to ketamine. Of the 23 reports found in fact, only 2 cases concerned improper use and, in particular, "Section 7" was completed in only one of these in 2015. However, this low number of reports is not in line with the data presented annually by the Anti-drug Department to the Italian government on the state of drug addiction. In 2013, the trend relative to the average consumption of ketamine was on the increase having gone from 2.9g per day for every 1000 inhabitants in 2012 to 3.3g in 2013 (Anti-drug Department, 2014). This seemed to affect central and northern Italy the most, in particular Florence (7.6g/day) and Bologna and Torino (6.6g/day). In 2015 it was reported that the National Health emergency services had dealt with a number of cases in 2014 which were difficult to identify from a clinical point of view and as a result, a specialist consultancy was requested from the Anti-poison Centre (CAV) in Pavia. Among these cases, 256 patients presented with symptoms which the CAV judged to be: a) caused by relatively unknown abusive substances; b) not strictly related to an abusive substance previously reported in the patient's history or c) resulting from the effects of stimulants or hallucinogenic substances, even without any patient history of the suspected use of abusive substances (Anti-drug Department, 2015). The main clinical symptoms which were registered by the emergency departments concerned the effects of stimulants (agitation/over-excitement, hallucination/delirium or tachycardia), associated in some cases with neuro-depression leading to coma. The main substances reported in the histories of the

256 patients were cannabis (51 cases) and cocaine (33 cases) while ketamine was cited in 20 cases. In another 5 cases, ketamine was found due to an in-depth clinical examination and a further investigation of the patient's history. Furthermore, in both 2013 and 2014, there were many cases (some extremely serious) of intoxication by ketamine. (Anti-drug Department, 2015).

Data resulting from an analysis of waste water carried out by Castiglioni and colleagues confirmed the ongoing constant use of ketamine (Castiglioni et al., 2015). This investigation was useful as it evaluated for the first time the pattern of ketamine use on a nationwide scale and it was thus possible to identify significant differences in various parts of the country. In the conclusion to the study, the authors state that the ketamine loads in urban waste water mainly come from human excretion and this enabled them to identify the progressive increase in ketamine use in recent years in Italy with differences in local consumption (Castiglioni et al., 2015). However, the fact that only 2 cases of ketamine abuse were found in the Italian database is in line with another study which analysed the entire pharmacovigilance database in Germany where until 2013 there were no reports concerning ketamine (Gahr et al., 2014). The author of this study also emphasised that this was in contrast with literature providing evidence of the abuse potential of ketamine (Ahmed and Petchkovsky, 1980; Critchlow, 2006).

With regard to the analysis carried out on the WHO database for this thesis, the cases which were precisely linked to the abuse or improper use of ketamine were then selected from VigiBase by means of the specific MedDRA preferred terms. Most of these came from the USA and Europe and involved males between the ages of 18 and 44 years. Even though the origin of these reports is in line with the WHO database, this differs from the data in literature on the subject which speaks of the widespread use of ketamine in Asia (Chen et al., 2009; Fang et al., 2006; Joe-Laidler and Hunt, 2008; Lua et al., 2003; Ng et al., 2010). The gender differences found in our analysis were also found in a study by Chen and colleagues on ketamine use in Taiwan (Chen et al., 2014). The ADRs in the 202 reports relating to ketamine abuse were in line with those reported in the literature on the subject in general, with the most frequent SOCs being nervous and psychiatric disorders (Morgan and Curran, 2011). The reactions concerning renal

and urinary disorders were also in line with the literature and this demonstrates that these problems must be taken into consideration (Cottrell and Gillat, 2008; Selby et al., 2008; Shahani et al., 2007). However, taking into account the elevated interest in this molecule, the reports in Vigibase are somewhat limited.

This analysis of the two databases (Italian and worldwide) should in any case be evaluated in the context of the issues surrounding the spontaneous reporting of ADRs. It is well known that the greatest weakness of the spontaneous pharmacovigilance system is under-reporting since not all ADRs are identified and reported (Hazell and Shakir, 2006; Lopez-Gonzalez et al, 2009; van der Heijden et al., 2002) and this affects the present study in the sense that there are fewer data. Furthermore, this system often contains limited clinical information and as a result in most cases it is impossible to ascertain the dosage regimen, the formulation, the dosing interval, the treatment duration, the weight of the patient and the results of biological tests. Additionally, the lack of denominator data such as the user population and drug exposure patterns may have influenced the analysis (Aagaard et al., 2012). Even though the spontaneous reporting methodology does not have the strength of evidence of clinical trials or cohort studies, it nevertheless generally allows a worldwide analysis of data to be carried out with respect to a larger number of patients and at a lower cost. Moreover, this study shows that, thanks to the new "Section 7" in the Italian spontaneous reporting system for ADRs, it is now possible to analyse reports relating to improper use quickly and accurately.

It should also be remembered that the main strength of VigiBase is that it covers many countries and all drugs over a longer period of time than other databases. Its main limit, instead, is the frequency with which the WHO database receives reports. This varies considerably between countries due to several technical issues: the various length of time that a country has been affiliated to the WHO programme, general knowledge of ADRs, public awareness of specific safety issues (i.e. specific monitoring programmes) and the attitudes of health professional to reporting ADRs (Bate et al., 2008). Despite these limitations, both these pharmacovigilance databases remain a valuable tool for defining the pattern of ADRs for drugs.

In any case, this analysis should be evaluated from the wider point of view of abuse potential and abuse liability. In the specific case of ketamine, it must be noted that it was introduced as an anaesthetic at a time when there were no studies on abuse potential and liability. However, cases soon appeared involving its improper use and abuse and a number of studies have confirmed the increase in its non-medical use (Dalgarno and Shewan, 1996; Morgan and Curran, 2011). Despite this, ketamine is still regarded as an essential medicine, even in situations with scarce facilities, and it represents a safe anaesthetic that does not depress respiration or the cardiovascular system (Burke et al., 2015).

The fact that there are also many clinical trials which indicate that ketamine is effective as an anti-depressant means that the aspects relating to its abuse should not limit its use as a pharmaceutical.

This is confirmed by various researchers who support the WHO analysis according to which the medical benefits of ketamine far outweigh any potential harm from recreational use (Taylor et al., 2016). In contrast, other researchers point out that the rapid proliferation of off-label ketamine administration in the absence of evidence of lasting therapeutic benefit or safety with long-term use is truly alarming (Newport et al., 2016). Confirmation was found also in the present study that there are no systematic safety data regarding long-term ketamine administration. It is debatable whether relying upon post-marketing surveillance in the aftermath of the proliferation of ketamine treatment centres to ascertain those risks will compromise public health, but doing so is certainly ethically dubious (Newport et al., 2016).

This is surely yet another limit relating to spontaneous reporting and it thus remains to be seen whether post-marketing surveillance can be of assistance in terms of providing information on the abuse potential and abuse liability of a drug, above all for new pharmaceuticals which act on the central nervous system.

In fact, the developers should assume that all compounds of this type require abuse liability assessment if mood-elevating, stimulant, sedative, or hallucinogenic properties are observed in nonclinical or clinical studies (e.g. locomotor stimulation or depression and clinical AEs such as somnolence, hyperactivity, euphoria or hallucination etc.) (Schoedel and Sellers, 2008;

Swedberg, 2013). Guidance on the evaluation of the abuse liability of drugs in the USA and Europe differ in various points of the process (e.g. in the mechanism for reporting the results in the submission dossier) (Calderon et al., 2015). Moreover, there is no universally accepted list of terms that are known to predict post-marketing abuse potential and liability. In order to protect public health, it is therefore fundamental that these terms are defined and that an abuse liability assessment is carried out early on in the drug development process. It is also certainly necessary for a post-marketing surveillance system to be implemented so that spontaneous reporting is rapid, sensitive and specific. However, the system should also guarantee a balance between the control of the potential abuse of a pharmaceutical and its proven efficacy and utility.

In conclusion, the results of the research which was carried out for this thesis have shown that while there are various publications which concern clinical studies on the efficacy of ketamine as an anti-depressant, there are no data in the literature on its safety with the result that it is not possible to create a safety profile relating to either its short or long term use. However, the analysis of spontaneous reports which was done, even though a number of limits were identified, confirmed that even low doses of ketamine cause ADRs involving nervous and psychiatric disorders, in addition to those which result from its anaesthetic use. On the other hand, post-marketing surveillance based on spontaneous reporting has not revealed any significant new information concerning the abuse of ketamine. In fact, even after the introduction of a new definition of ADR, reports of ketamine abuse in Italy and worldwide have not increased. Those profiles which are noteworthy regard conditions which derive from abuse liability, even though the reactions reported are very few. In the area of pharmacovigilance, some further implementations are necessary in order to provide more support and useful information concerning drug abuse liability.

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