Journal Homepage: - www.journalijar.com
INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)
Article DOI: 10.21474/IJAR01/8393
DOI URL: http://dx.doi.org/10.21474/IJAR01/8393

RESEARCH ARTICLE

TRAMADOL ABUSE.

Saleh M Kh E A Alkhubaizi.
Department of Medicine, Adan Hospital, Kuwait.

Manuscript Info

Manuscript History
Received: 12 November 2018
Final Accepted: 14 December 2018
Published: January 2019

Key words:-
Tramadol, Abuse, Neurological Pathways, Medical Uses, Reward pathway.

Abstract

The study of tramadol has increased during the last decades, as tramadol has a potential risk to both an individual and the society he/she lives in. However the concept of using tramadol as a painkiller has become a revolution recently. Because of this, all the efforts have been applied in studying this therapeutic drug and the factors for its addiction and abuse. The abuse of the drug among physicians and patients required the study of the physiology and the chemical component of the drug and the regulation of the neurotransmitters through the central nerves system to limit the addiction of the drug. Therefore, knowledge about the chemical and central nervous system cascade will help putting a variety of strategies to tackle the abuse of the drug and its reward pathways for addictive, dependent, and tolerant patients. Moreover knowledge of the symptoms, side effects, and the clinical pharmacology of the drug, will limit the risk factors of the drug. Unintentional abuse or misuse is also a major problem for Tramadol users

Introduction:-

Origin of Tramadol

This essay discusses various aspects regarding the abuse of Tramadol, which was a drug first produced in 1962 by Grünenthal GmbH, a major pharmaceutical company established in post World War II Germany in 1946 (“History of the Drug” n.d.). In a world in which various painkilling medications already existed, the new and revolutionary attribute of Tramadol was its “double action” mechanism that changed the way people could deal with pain. Since then, Tramadol has been licensed to other companies around the world (also under various generic names) and has been improved and made available in various forms. Using its full name Tramadol hydrochloride, the drug can combat mild to severe pain by directly targeting the body’s central nervous system. It is typically used to treat conditions such as rheumatoid arthritis and fibromyalgia.

Tramadol: Abuse, Addiction, Dependence and Tolerance definitions

Unfortunately, the use of Tramadol can also produce side effects and can be addictive. In fact the American Food and Drug Administration (FDA) – in conjunction with a major pharmaceutical manufacturer – found it necessary in 2010 to circulate a Warning notice to all Healthcare Professionals (“Important Drug Warning” May 2010) about the prescription of Tramadol tablets (under the brand name Ultram). The document includes explanations regarding abuse, addiction, dependence and tolerance.

Corresponding Author:-Saleh M Kh E A Alkhubaizi.
Address:-Department of Medicine, Adan Hospital, Kuwait.

Abuse
Addiction is described as a "primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations" ("Important Drug Warning" May 2010).

Addiction
Taking the particular case of drug addiction, the document states that it is "characterized by behaviors that include one or more of the following." It lists impaired control over the use of drugs, using drugs compulsively and with craving, using them for purposes other than for medical reasons, and continuing to use them even if aware they may be causing harm. The text states that it is treatable on a multi-disciplinary basis, though relapses are common. It also states that a common behavioral trait among drug addicts and abusers is to use "drug-seeking" tactics. These may include various strategies to obtain drugs such as making an "emergency" call or visits approaching the office at closing time, refusing to be examined or to provide medical records or a doctor's name, repeatedly "losing" prescriptions or even tampering with them. It seems that what is known as "Doctor-shopping" is a common practice for such people.

Dependence
The FDA document points out that abuse of drugs are different to and separate from either physical dependence or tolerance. It also states that medical professionals should note that a case of addiction may not always be accompanied by a tolerance of the drug(s) or any symptoms of physical dependence. In the particular case of Ultram (Tramadol), abuse is possible without these aspects. In such instances, the use is usually for "non-medical purposes, often in combination with other psychoactive substances."

Tolerance
Tolerance is defined in the FDA document as "the need for increasing doses of drugs to maintain a defined effect such as analgesia." It describes physical dependence as being manifested by the occurrence of withdrawal symptoms when the drug is abruptly discontinued, or its effect is blocked by "administration of an antagonist."

Why Tramadol is Prescribed as the Drug of Choice General
Designed to relieve what is termed "moderate to moderately severe" pain, Tramadol extended-release tablets or capsules are selected as an appropriate drug for patients who are likely to require pain-relieving medication "around the clock" ("Tramadol" Oct. 2013). Classified as an opiate, Tramadol works by altering the response of the brain and the body's nervous system to pain.

Martinez (n.d.) notes that, in addition to inducing those altered responses, Tramadol can block the receptors in the brain that sense pain. She also notes that its use is often selected for applications where the pain relief requirement is relatively short-term, because of its known propensity to be addiction-forming and then becomes difficult to give up.

Tramadol Is Not a Controlled Substance
Another powerful reason why Tramadol is widely prescribed by doctors is that in many countries / states it is not classified as a controlled substance. Furthermore, the literature generally describes it as low risk for addiction. That means that the prescribing doctors are not required to maintain detailed records, as they would for drugs classified formally as addictive ("Tramadol Addiction" Jan. 2013). However, the picture has changed in recent years as doctors in various countries have come to realize that there is a potential addiction problem. As the article reports, various US states have decided to categorize it as a Schedule IV Controlled Substance, and there is a real addiction problem reported in other countries like Egypt, for example.

Tramadol Advantages
Notwithstanding those potential problems, many consider Tramadol an ideal solution for their condition. "The Pros and Cons of Tramadol" (n.d.), enumerates some of its advantages:

1. It provides effective treatment for moderate or severe pain levels, irrespective of its cause, although studies have indicated that it does work better for some types of pain such as multiple sclerosis, motor neurone disease, etc.
2. It works equally well with either chronic or acute pain, so can be prescribed for pain of a temporary nature, such as after an injury or following surgery.
3. It has a broader permitted age range than many drugs; anyone over 16 can be prescribed it.
4. Although circa 70 percent of users experience some form of side effects, they are mostly not long-lasting, nor severe.

Tramadol Abuse

"Recent research shows that tramadol has greater potential to be abused and to cause overdoses than was believed when it first appeared on the U.S. market in 1995" (Fauber, Dec. 2013). According to his report, the FDA may have been mistaken in not including Tramadol in the scope of the Controlled Substance Act. The FDA overlooked research indicating it (potentially) could be abused. The decision made by the FDA to approve Tramadol was based primarily on its injected mode of use, and on information obtained from Europe, where Tramadol had been in use for much longer. However, the FDA were also in possession of research which indicated that if Tramadol were to be administered orally in high doses to opioid abusers, it would produce effects of an opiate nature similar to OxyContin, which Fauber claims is "one of the most abused drugs in America." He notes that the FDA had asked the company marketing Tramadol in the US to finance a committee paid to look for abuse problems that might lead to Tramadol needing to be reclassified as a controlled substance, but "That never happened." Now – 18 years after its US launch – the DEA (Drug Enforcement Administration) has proposed implementation of that reclassification at the federal level. Meanwhile, no less than 10 US states have independently taken that step already.

As a point of interest, a Canadian document "Review of Abuse Risk for Tramadol." (2006-7), includes a Figure that illustrates clearly how when Tramadol was "scheduled" (was made a controlled substance) in Egypt in 2002, the number of prescriptions for it plummeted by 95 percent. Then when it was de-scheduled two years later, the volume of prescriptions was restored to at least the previous levels. That Figure is reproduced at Figure 3.

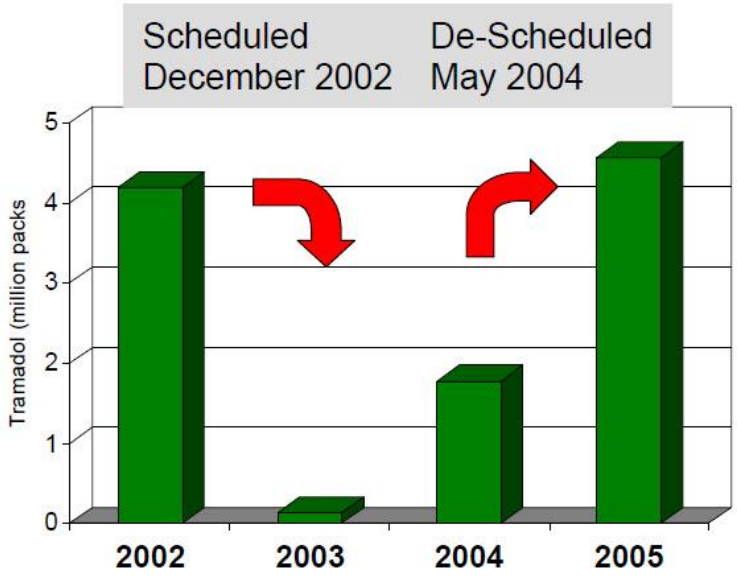

Figure 3:-Impact of Scheduling and De-scheduling of Tramadol in Egypt(Extracted from: "Review of Abuse Risk for Tramadol.")

According to Fauber, these changes are not before time. He cites a joint investigational analysis undertaken by the Milwaukee Journal/Sentinel and MedPage Today which found that there has been a dramatic increase in the use of Tramadol since 2008. According to data obtained via IMS Health – a market research company – there were 25 million Tramadol prescriptions in 2008, but that number had increased to almost 40 million by 2012. Whilst the statistics arising from that analysis do not necessarily reveal the extent of use of Tramadol that was entirely abusive, they do make worrying reading. For example, it was reported that, in 2011 alone, there were 20,000 emergency department visits across the nation, which were linked to Tramadol. And in that same year in Florida, there were 379 deaths resulting from Tramadol overdoses – an increase from just 106 eight years earlier. According to Milwaukee medical records, between 2010 and October 2013, 20 people in Milwaukee County died as a result of a Tramadol-related drug overdose. In the majority of those cases, several opioids had been taken, including Tramadol.

Fauber states that the important evidence overlooked when approving Tramadol in the US was that a John Hopkins University study had shown that high oral doses of Tramadol taken by opioid users acted on the body in a much different way than if administered by injection. He also noted that the effects are similar to those from oxycodone at

high dosage. Taken orally, the liver transforms Tramadol into a metabolite (M1) which can attach to opioid receptors in the brain and activate them. It is the M1 that is thought to induce the mentioned effect. Fauber quotes Sharon Walsh, a University of Kentucky College of Medicine opioid researcher, who claims that the Hopkins study provided significant evidence regarding the abuse potential of Tramadol. Given that evidence, it would be unlikely that the FDA would approve Tramadol in the classification of non-scheduled drugs. However, at the time of the FDA approval, drug abusers predominantly used injections as their method of choice, prior to the dramatic increases in drug abuse by pills in later years.

Fauber also reports that because the FDA had concerns at that time about potential abuse, they appointed an "independent steering committee" to monitor Tramadol as part of the FDA's approval process. However, the company marketing the drug in the US not only funded that committee's work, but also paid its members consulting fees – total costs circa $15 million annually. Fauber quotes Andrew Kolodny MD, a New York specialist in addiction, as stating that: "There was absolutely nothing independent about this group."

Fauber notes that large numbers of people use oral Tramadol for recreational purposes, and – according to the DEA – 2.6 million individuals aged 12 or over used it in 2011 for "nonmedical purposes". Further, the DEA stated that the most common abusers of Tramadol are "addicts, chronic pain patients, and health professionals." There have for some years been indications of Tramadol being abused, but Ortho-McNeill, the company that markets Ultram, has resisted efforts for it to be categorized as a controlled substance.

According to the American Psychiatric Association, symptoms of Ultram (Tramadol) abuse include at least one of the following over a period of one year ("Tramadol Abuse Signs, Symptoms and Addiction Treatment" n.d.):

1. Repeated failure to fulfil obligations relating to work, school or in the home
2. Use in potentially physically hazardous situations. For example while driving a vehicle or operating machinery
3. Legal problems arising from its use, such as a drug-related arrest
4. Continuing to use it, even though there have been negative consequences of social or interpersonal nature.

That article describes the specific effects of abuse as varying per individual, but which may include: "nausea and vomiting, euphoria, shallow breathing, dizziness, constipation, and drowsiness." As the body becomes accustomed to the drug, increasing physical tolerance to it means that the body needs more of it just to reproduce that original, desired effect. To give some idea of the scale of the abuse problem, the same article provides some Tramadol facts and statistics:

1. FDA data indicates that more than 760 cases of Tramadol abuse and 480 incidences of Tramadol withdrawal were reported between 1995 and 2004.
2. According to studies, Tramadol abusers are most likely to be patients with chronic pain, abusers of other narcotics, and healthcare professionals.
3. Tramadol is not listed in the Controlled Substances Act and is, therefore, not classified as a narcotic, even though as an opioid it has abuse potential.
4. Tramadol dependence is most prevalent in long term users, who have been taking it for legitimate medical purposes.

Also mentioned in that same article is the outcome of a study by the United States Department of Health and Human Services (HHS), which found that circa 44 percent of six million new users of prescription drugs were under 18, indicating a trend of increasing drug use by adolescents. Hence drug prevention needs to be targeted at the younger generation.

Unintentional Abuse

Unintentional abuse or misuse is also a major problem for Tramadol users. A CDC Fact Sheet "Drug Overdose in the United States: Fact Sheet" (updated Feb. 2014) reports that, in 2010, 75 percent of the 22,134 US deaths due to drug overdose involved opioid analgesics.

The same problem was reported in the UK. Waters (Apr. 2013) discusses cases of unintentional misuse and other aspects of Tramadol, which in the United Kingdom is a cheap remedy, costing the National Health Service (NHS) just £1.99 (about $1.20) for 100 tablets.

Waters reports on the case of Lizz Bowker, a 57-year old mother of three, who had been taking Tramadol for about a year to provide pain relief for her back pain and leg ulcers. She accidentally took too many tablets (just two extra compared with her usual eight 50mg tablets a day) and died as a result. Her husband of a 38-year marriage is quoted as saying "I was devastated – I'd been laughing and joking with her 20 minutes before and she'd showed no signs of being unwell" (Waters, Apr. 2013). He had been away from her side for only six minutes.

As Waters states, the tragedy is that this was not the only isolated case, but it also highlights the dangers of Tramadol, which is often considered as "the safer option." She reports that UK prescriptions for it (including other brand names such as Zydol and Zamadol) have increased from under six million in 2006 to over 11 million by September 2012. Waters notes that although many doctors consider Tramadol to be one of the weaker opioids, it carries the same overdose risk as morphine. As well as acting directly on the body's central nervous system, it causes enhanced effects of serotonin and noradrenaline, which are described as "brain messengers." It is this dual action which increases the probability of unintended interactions with other medications or substances providing a sedative effect. That in turn can affect the breathing process and perhaps cause death. Hence Tramadol should not be taken by someone who is also taking other medications such as: sleeping tablets or antidepressants or tranquilizers, or any painkillers that act directly on the brain, or who is currently affected by consuming alcohol. Waters reports that even though these interactions are well known, there are patients who are prescribed such combinations of medications. As a consequence of all these factors Tramadol overdose deaths in the UK have increased from just one in 1996 to a 2011 total of 154. In that period, it caused over 500 fatalities. It is not known exactly how many of those deaths were considered to be accidental.

Hom (Nov. 2013) cautions that although Tramadol is not classified in most US states as a controlled substance (as mentioned earlier) it nonetheless can still be abused. She also warns that whilst Tramadol tablets are designed for oral use; they should not be crushed to be used for inhaling or injecting the drug. "Snorting" it does increase the intensity of the perceived effects, but it also results in large doses of it entering the bloodstream, increasingly potentiate for overdose and potentially causing adverse outcomes such as seizures. The practice can also cause breathing difficulties, comas, hallucinations and even cardiac arrest.

Hom also reiterates what other observers have stated; i.e. that the number of incidences of Tramadol overdose has increased over the past 20 years. She attributes that increase to health professionals viewing Tramadol as a "safer opioid", causing patients to ignore or minimize the importance of instructions regarding dosage restrictions or warnings about possible interactions with other drugs. As a consequence, tolerance to the drug can progressively increase, making ever higher doses unsafe.

Although Tramadol is for the most part used with few problems, abuse is nonetheless a significant associated risk. Its addictive properties have prompted users to progress to using it for recreational purposes, which has often resulted in "highly damaging effects" ("The Tramadol Effect" Nov. 2013). The article points out that Tramadol – unlike a number of other painkilling medications – is not commonly thought of as a drug for recreational use. However, following its use as prescribed, some patients progress to using surplus remaining tablets recreationally, while others use it for that purpose, simply because they had enjoyed the initial effects it had produced. According to the article, that is where the abuse starts. Because of the changes it induces in the brain, stopping its use is not just a case of no longer taking the tablets, because the brain has become dependent on Tramadol. The article notes that as with other painkilling medications such as Vicodin, the most euphoric feelings come from its first use, and then subsequently the "high" is not so pronounced. As a consequence, users are continually striving to recapture that pleasurable effect, which can lead to "a perpetual spiral of abuse and withdrawal."

According to "The Consequences of Tramadol Addiction", (Nov. 2013), most doctors prescribe Tramadol and similar painkilling medications for their patients because they believe there are more benefits than drawbacks. The reality is not so straightforward, nor is that any form of guarantee, being dependent on patients taking the medication as directed. Those who exceed the prescribed dosage, or "snort" the crushed tablets, or who over a long period abuse the drug, are placing themselves at daily risk of death. Approximately 20 percent of people taking prescribed medications become addicted.

Details of some of the effects of Tramadol abuse are described in "The Physical, Mental, and Emotional Impact of Tramadol" (Nov. 2013). The article states that because Tramadol acts directly on the brain, the mental impact of addiction to it is the most significant effect. It continues, "The physical symptoms one sees in a Tramadol abuser are

relatively insignificant when compared to the inner turmoil experienced by those who habitually use the substance." It is noted that because a commonly-occurring side effect of Tramadol is suddenly developing aggression, if that is coupled with a demonstrated urgent need to increase the intake of Tramadol, the individual concerned is heading for trouble. Abuse can cause the user to be confrontational when interacting with friends, family members, or even with pharmacists if they indicate they suspect possible addiction. Another serious concern mentioned in the article is that of the real possibility that Tramadol abuse can result in people considering self-harm including suicide. Preemptive intervention in such cases is made virtually impossible, as most abusers maintain the secrecy of their habit. The fundamental problem is that because the brain is affected / altered by Tramadol, the user begins to believe that continued use is essential. In extreme cases, a user may deal with opposition from well-meaning others by deciding that suicide is an easier option than recovering from the addiction.

The same article describes the emotional impacts of Tramadol abuse as "a double-edged sword." While the user/abuser is of primary concern, their abuse has major effects on their caring friends and family. It helps to be observant about a loved one's mood swings or other behavioral and/or physical changes, but to be successful in helping someone in this situation usually requires professional help. In many cases, those close to the abuser can become angry with them because of the effects of their behavior is having on the lives of others, such as increased stress and worry. However, the best approach in such cases is not to express that anger, but to try to intervene in a way that does not add to the abuser's feelings of guilt, and to take positive action to obtain help for them.

Managing to withdraw from this addiction is not easy states Lee (2011), states that: "many thousands have found that the medication they turned to for assistance has created a problem with addiction far greater than the pain it was initially prescribed to manage." Further, he describes detoxification and withdrawal as a long, painful and difficult process, in which the peak of the withdrawal-induced problems occurs within a day or so of stopping Tramadol, and lasts for three to four days at that high level, then progressively tails off for perhaps a month overall. Included symptoms produced can be "nausea, vomiting, leg restlessness, anxiety, depression, pain and a real risk of seizures" (Lee, 2011). Additionally, Lee advises not to try withdrawal on a "cold turkey" basis, which can increase the risk of seizures. Withdrawal should always be undertaken with medical help and supervision. He adds that to ensure abuse and addiction are not repeated, successful detoxification should always be followed by professional drug treatment therapy.

Some International Perspectives on Tramadol Abuse

Radbruch et al., offer a German view of the abuse of Tramadol (2013). According to their study, reported in *Substance Abuse*, Tramadol was found (in both animal and human studies) to have a low potential for misuse, abuse and dependency. Those findings were also borne out by inputs from other (German) sources such as pharmacies and addiction counseling centers.

A somewhat contrasting view originated from a study conducted by Zabihi et al., in Northern Iran, in 2007-2008. Their study was implemented due to suspicions that patients visiting pharmacies in Babol, in Northern Iran might be abusing Tramadol. Over a six-month period, every patient who requested Tramadol was required to complete a questionnaire (under supervision by a pharmacist) designed to detect potential drug abuse. The outcome of the study was that from the 162 results obtained, around two thirds indicated criteria for addiction. Of the total number of patients, 89 percent were younger than 30, and 55 percent were below 18. Almost two thirds reported drug abuse or addiction in their history, especially those not presenting prescriptions. The conclusion was that there was a high potential for Tramadol abuse, and a high prevalence of individuals under 18, which the authors see as possibly being a worldwide trend.

A highly detailed Canadian study documented in "Review of Abuse Risk for Tramadol" (2006-7) agrees with the findings of the German study mentioned above; i.e. that the abuse risk is low. In Section 5.3 Conclusion (pp.27-28), the verdict given is that "The collective data in animal and human studies conclusively demonstrate the low abuse liability of tramadol." It also states that data indicate that there is a low risk of developing tolerance and dependence. Further, it is noted that in comparison with morphine, withdrawal from Tramadol was "mild to moderate." To demonstrate the credibility of these findings, the paper refers to the FDA's "Draft Guidelines for Abuse Liability Assessment", which acknowledged that good quality epidemiological data can be a good indicator of abuse potential. It is noted that such data available for Tramadol spans 28 years.

Another more pessimistic view comes from Fawzi (2011), describing the situation prevailing in Egypt, and arising from a 2010 study of patients at the Poison Control Center Ain Shams University (PCC ASU) Egyptian Hospitals. In contrast to the Canadian opinion expressed, he says: "An increasingly alarming phenomenon of tramadol drug abuse has been demonstrated in the Egyptian community." Fawzi attributes part of the cause to the fact that Tramadol is cheaper and more widely available than other abused drug types. He also claims its popularity has increased because it is widely used "as a remedy for premature ejaculation and for extended orgasm and to increase sexual pleasure as promoted in many online drug stores and media" (Fawzi, 2011). He also blames the amount of abuse on the fact that when "Ultram" was first marketed, the manufacturer claimed it "produced only very weak narcotic effects." As a consequence, inadequate labelling and ignorance of its potential for abuse encouraged physicians to prescribe it widely, resulting in the abuse that has occurred.

Tramadol Abuse and Dependence among Physicians

As previously mentioned, with reference to the article "Tramadol Abuse Signs, Symptoms and Addiction Treatment" (n.d.), healthcare professionals are one of the groups in society susceptible to becoming abusers of Tramadol. That view was borne out in a research letter by Skipper et al. (four health professionals) published in the Journal of the American Medical Association in 2004. The letter notes that in common with some other opioid pain medications, Tramadol was regarded as having low abuse liability when it was introduced, but has since had packaging warnings regarding abuse raised on three occasions (p.1818). The authors of the letter cite earlier reports suggesting low abuse liability as being "problematic" (unreliable). In contrast, their own study (focused on physicians in recovery programs in Alabama and Michigan), suggests that Tramadol's abuse liability is on a par with a number of other drugs and higher than (for example) codeine, morphine, and oxycodone (p.1819). Overall, the study found that the incidence of opioid abuse was second only to alcohol abuse. The tabulated findings of the study are reproduced at Figure 1.

Table. Drugs Abused by Physicians in Alabama and Michigan, by Category

	No. of Mentions		
Substance	Alabama	Michigan	Total
Alcohol	191	198	**389**
Opioids	190	146	**336**
Hydrocodone	86	53	**139**
Meperidine	25	10	**35**
Tramadol	23	10	**33**
Fentanyl	11	16	**27**
Codeine	11	13	**24**
Propoxyphene	10	6	**16**
Oxycodone	10	5	**15**
Morphine	8	4	**12**
Butorphanol	5	7	**12**
Pentazocine	0	9	**9**
Other	0	14	**14**
Sedatives	59	10	**69**
Stimulants	34	21	**55**
Marijuana	12	11	**23**

Figure 1:-Drugs Abused by Physicians in Alabama and Michigan, by Category(Extracted from: "Tramadol Abuse and Dependence Among Physicians.")

All the physicians included in the study had been referred to recovery programs due to previously expressed concerns about substance abuse, and all of them had been evaluated, treated, and monitored. Of the total of 872 physicians' records reviewed, 595 of them included mentions of drugs. And Tramadol was involved in 10 percent of all opioid cases. A total of 33 physicians involved with Tramadol, 32 were diagnosed as being substance dependent, and one as being involved in substance abuse. The authors note that there were relatively frequent mentions of Tramadol as a drug involved in abuse by the physicians, only rarely was it their first choice drug. It was felt that the anomaly was caused by its intrinsic level of abuse liability being higher than previously had been assumed. Another reason could have been that it was readily available and – crucially – was not classified as being within the scope of the Controlled Substances Act, thereby making it a more attractive option. Toxicity concerns are linked not only with the drug's abuse potential, but also to issues related to excessive dosage, including seizures, respiratory problems and the real risk of an overdose proving to be fatal. The authors conclude by noting that although their study did not examine the statistical relationship between the numbers of physicians developing either abuse or

dependence and the specific choice of opiate. However, the study has shown that abuse of Tramadol has shown up with sufficient frequency to flag physicians that they should ensure they are fully aware of the risks involved.

Physicians being considered to be in a higher risk group of the population for Tramadol abuse is a phenomenon also noted by Green and Muskin (2013) in their book *The Neuropsychiatry of Headache* (p.67). It mentions that abuse of Tramadol among physicians ranks third (after hydrocodone and meperidine) for the 10 percent of physicians who admit to abuse.

Prevalence of Tramadol Abuse

A study undertaken by Adams et al. and published in the *Journal of Pain System Management* in 2006 set out to determine the prevalence of abuse of or dependence on various opioid analgesics in chronic pain patients. The study drew comparisons between the abuse of Tramadol and "non-steroidal anti-inflammatory drugs (NSAIDS), and hydrocodone-containing analgesics in patients with chronic noncancer pain (CNP)" (Adams et al., 2006). The study comprised three patient groups: the first comprised of patients prescribed just Tramadol; those in the second group were patients randomly given either NSAIDS or Tramadol, and those in the third group were randomly prescribed either hydrocodone or Tramadol. Each of the study investigators (physicians) was issued two boxes of prescriptions that were randomized in such a way that one of every four was a Tramadol prescription. After deciding which was therapeutically appropriate, the physician selected the appropriate box, opened the next envelope and filled out the prescription enclosed. After that initial (random) phase, the physicians were able to prescribe whichever medication was therapeutically the most appropriate. The study involved 11,352 patient subjects (as Figure 2 illustrates), who were each assessed by structured questionnaires during a series of nine interviews conducted during a period of one year. The interviews were used to determine those abusing the drug. Factors taken into account were: those increasing the dosage without approval of their physician, using it for unintended purposes, inability to cease using it, and withdrawal. Scores for at least one instance of abuse during the one year follow-up period were: NSAIDS – 2.5 percent; Tramadol – 2.7 percent; hydrocodone – 4.9 percent. When more than one factor was used to measure persistence, the figures were: NSAIDS – 0.5 percent; Tramadol – 0.7 percent; hydrocodone – 1.2 percent. The conclusions arising from the study were that the prevalence of abuse / dependence was about equal for Tramadol and NSAIDS, with both of those being significantly lower than the figures for hydrocodone.

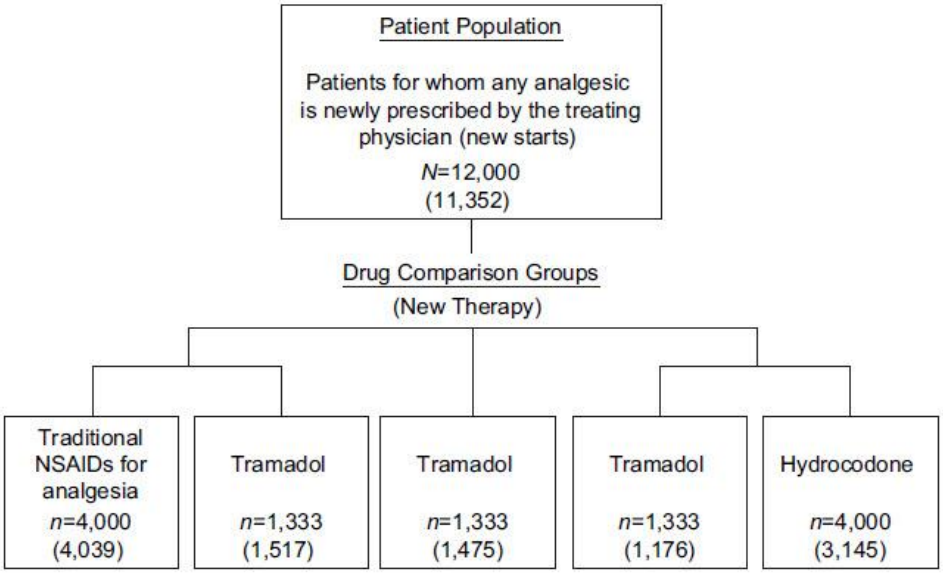

Figure 2:-Subject population, drug comparison groups. Numbers in parentheses are the actual numbers achieved vs. the target numbers.(Extracted from: "A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain.")

The Physiology of Tramadol

Chemical Composition

The full chemical name for tramadol hydrochloride (Ultram®) is "(±)*cis*-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride" ("Ultram" Jun. 2013). Figure 4 depicts its structural formula. It is a white, odorless powder which is water-soluble, with a pKa of 9.41. The white-colored Ultram® tablets each contain

50 mg of the active ingredient, and "Inactive ingredients in the tablet are pregelatinized corn starch, modified starch (corn), hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, titanium dioxide and carnauba wax" ("Ultram" Jun. 2013).

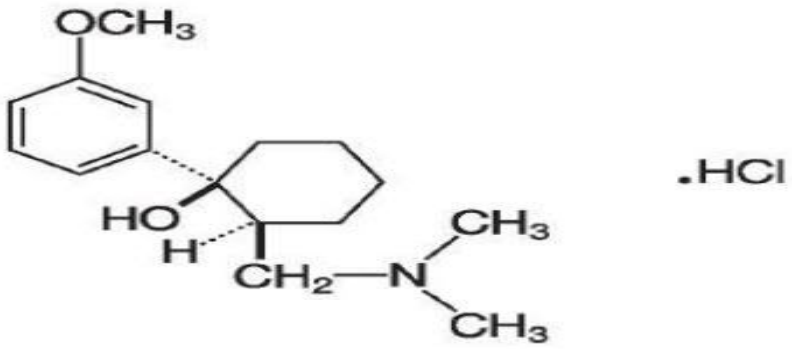

Figure 4:-Tramadol Structural Formula(Extracted from: "Ultram")

Clinical Pharmacology

Tramadol is a "centrally acting synthetic opioid analgesic" ("Ultram" Jun. 2013). It is believed that there are two complementary mechanisms involved in its mode of operation, although the process is not known with certainty. The first of the two mechanisms is "binding of parent and M1 metabolite to μ-opioid receptors." The second is a "weak inhibition of re-uptake of norepinephrine and serotonin." The analgesic effect begins around one hour after taking the tablet and peaks after two to three hours. In addition to the desired analgesic effect, Tramadol (like other opioids) can produce a range of other effects, which might include: "dizziness, somnolence, nausea, constipation, sweating and pruritus" ("Ultram").

Brain Pathways

It is believed that substance abuse stimulates something in the brain called "a common reinforcement pathway" which comprises structures forming part of the central nervous system (CNS), and "endogenous neurotransmitters" communicating with them ("Neuroanatomy and Physiology of the 'Brain Reward System' in Substance Abuse," n.d.). That combination is also referred to as the "reward pathway." Figure 5 is extracted from the above-referenced article, illustrates the "reward" area in the brain. The reward pathway has evolved to promote essential survival activities. The article also suggests that the mechanisms involved in drug abuse can be compared with viruses in the way that they "take over" cell functions, modifying those that are important in the brain, causing behavioral modifications. The drugs utilize the reward pathway, causing it to operate to promote further use of the affecting drug. The extent of those effects depends to some extent on individual characteristics, including inherited neurochemical composition. Those who possess genetic immunodeficiencies inherited from their parents are more susceptible than others. When the neurons of the reward pathways are stimulated by drugs they release chemicals which produce feelings of wellbeing, much as they do in association with basic species survival activities such as those involving sexual activity and feeding. The problem occurs with repeated use of drugs when the brain's reward system becomes monopolized by the stimulation from the drug, overriding other "normal" activities.

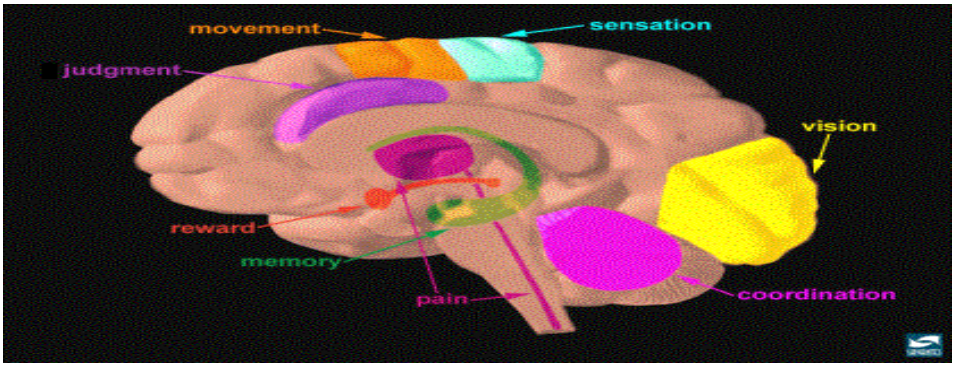

Figure 5:-Functional Areas of the Brain (Extracted from: "Neuroanatomy and Physiology of the 'Brain Reward System' in Substance Abuse."

Reward Pathway Structures

Anatomically speaking, the reward pathway structures are affected by other neurochemicals and other areas of the brain, with which the reward pathway has interrelationships ("Neuroanatomy and Physiology of the 'Brain Reward System' in Substance Abuse," n.d.). Although some of the factors involved are either unknown or have not been fully determined, this description attempts to provide a basic overview of how evolution has caused the drugs of abuse to stimulate and "take over" the reward pathway structures. The most important of these structures are located in a part of the brain known as the limbic system, which is primarily associated with brain functions including the maintenance of physiological equilibrium, memory, learning, and emotion. It is also the driver for aspects of sexual and feeding behaviors, and of motivational functionality.

Particularly important parts of the limbic system are the *nucleus accumbens* (NA), which is the area targeted by drugs of abuse, and the *ventral tegmental area* (VTA). The VTA is the brain area stimulated by opiates such as Tramadol. Other structures interact with the reward pathway, including "the endocrine and the autonomic nervous systems [which] interact via the hypothalamus, an integral part of the limbic system, and the pituitary ("Neuroanatomy and Physiology of the 'Brain Reward System' in Substance Abuse," n.d.). The article notes that the hypothalamus is influential in many brain functions including those of eating and drinking as well as sexual behavior. It is also the area affecting pleasure, anger and hostility. It can be considered as the autonomic nervous system control center, which links both body and environmental stimuli with the reward pathway

The Reward Pathway: Molecular Physiology

Dopamine is the main neurotransmitter associated with the reward pathway, in that all drugs of abuse cause an increase of dopamine levels, whilst drugs not abused do not have that same effect. Serotonin is also thought to play its part, by affecting the amount of effort the user is prepared to make in pursuance of obtaining the wanted drug, although the relationship is not straightforward, and serotonin is also understood to affect the reward pathways via mechanisms / receptors in other brain areas.

Another of the brain's neurotransmitters affecting dopamine levels is GABA (gamma - aminobutyric acid), which is found in numerous areas of the brain. Drugs of abuse cause the release of GABA to be inhibited, allowing more dopamine to enter the reward system. Those higher levels of dopamine produce the sensations of euphoria or wellbeing. Other effects of GABA in interacting with the reward pathways are reductions of anxiety and inhibitions.

Endorphins are another influence on the brain's reward pathways. These are endogenous proteins which can have motivational effects on behaviour, causing increased dopamine levels in the reward pathways of the brain.

Actions of Opiates in the Brain

Because GABA neurons inhibit the generation of dopamine in the VTA, when their production is restricted by the effects of opiates, dopamine levels rise in the reward pathways. "Numerous studies support opiate action in key structures of the reward pathway" ("Neuroanatomy and Physiology of the 'Brain Reward System' in Substance Abuse," n.d.).

Medical Uses of Tramadol

General

As mentioned previously in this paper, the general purpose of Tramadol is to relieve or alleviate pain, by changing the way the body senses or reacts to pain. Essentially, it blocks the normal operation of pain receptors in the brain. This section of the paper describes some of the most common conditions for which Tramadol is prescribed.

Bone and Leg Disorders

Fibromyalgia is a chronic condition that is characterized by widespread areas of muscular pain and sometimes areas of particular tenderness. Tramadol can also be used to alleviate bone pain (e.g. osteoporosis-related) or pain resulting from physical injury. Osteoarthritis or arthritis patients may also be prescribed it, as might individuals suffering from severe cases of restless leg syndrome ("Uses and Medical Applications of Tramadol" 2012).

Gastroesophageal Reflux Disease (GERD)

GERD or acid reflux is a condition in which the stomach's acidic contents can be regurgitated into the esophagus, causing a burning sensation there. The resultant discomfort can be eased by Tramadol ("Uses and Medical Applications of Tramadol" 2012).

Pain of a Temporary Nature

Short term or temporary pain is often treated by prescribing Tramadol. Examples are following surgery or for individuals suffering broken bones or trapped nerves. Although it can also be prescribed for those suffering chronic pain, it must be noted that it is preferred for short-term use due to its potential for addiction, which may then be followed by difficulties of withdrawal ("Uses and Medical Applications of Tramadol" 2012).

Head Pain

Tramadol may be prescribed for patients who experience frequent headaches or "debilitating migraines ("Uses and Medical Applications of Tramadol" 2012).

Other Medical Applications

As reported earlier in this paper in some regions of the world including the Middle East, Tramadol is popularly used "as a remedy for premature ejaculation and for extended orgasm and to increase sexual pleasure as promoted in many online drug stores and media" (Fawzi, 2011).

Conclusions:-

From the information compiled, it is evident that whilst Tramadol can be effective in treating the symptoms of pain on a short-term basis, longer-term use carries a significant risk of addiction – a risk that appears to be have been seriously understated by the drug manufacturers, and not appreciated until later by bodies such as the FDA. There is a suggestion in various quarters that by minimizing the stated addiction risk, the drug was kept off the FDA Controlled Substances list (and the equivalent in other countries), thereby making it easier for physicians to prescribe, due to a much lower requirement for detailed record-keeping. Further, sales volumes of Tramadol would be much lower if it was scheduled as a controlled substance, as was clearly demonstrated (in Egypt), when the drug (Ultram) was scheduled in 2002 then de-scheduled two years later (Refer to Figure 3). Experiences in recent years have shown that Tramadol does indeed carry a real risk of addiction, and that physicians are a high risk group in that respect.

References:-

1. Adams, E., H., Breiner, S., Cicero, T., J., Inciardi, J., A., Schnoll, S., H., Senay, E., C., and Woody, G., E. (2006). "A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain." *The Journal of Pain System Management. 2006 May; 31(5):465-76*. Available at: http://paincenter.wustl.edu/c/basicresearch/documents/cicerojpain2006.pdf
2. "Drug Overdose in the United States: Fact Sheet." (Updated Feb. 2014). *Centers for Disease Control and Prevention (CDC)*. Available at: http://www.cdc.gov/homeandrecreationalsafety/overdose/facts.html
3. Fauber, John. (Dec. 2013). "Killing Pain: Tramadol the 'Safe' Drug of Abuse." *MedPage Today*. Available at: http://www.medpagetoday.com/PainManagement/PainManagement/43554
4. Fawzi, Marwa, M. (2011). "Some medicolegal aspects concerning tramadol abuse: The new Middle East youth plague 2010. An Egyptian overview." *Egyptian Journal of Forensic Sciences, Volume 1, Issue 2, Pages 99-102, June 2011*. Available at: http://www.ejfs.org/article/S2090-536X(11)00030-X/fulltext
5. Green, Mark, W., and Muskin, Philip, R. (2013). *The Neuropsychiatry of Headache.* Cambridge University Press. Cambridge, UK. Print.
6. "History of the Drug." (n.d.). *Buy Cheapest Tramadol*. Available at: http://www.buycheapesttramadol.org/intro.htm
7. Hom, Elaine, J. (Nov. 2013). "Tramadol: Dosage & Side Effects." *Live Science*. Available at: http://www.livescience.com/41174-tramadol.html
8. "Important Drug Warning." (May 2010). *Food and Drug Administration (FDA).* Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM213265.pdf
9. Lee, John (Ed.). (Updated Sep. 2011). "Ultram Addiction." *Choose Help.* Available at: http://www.choosehelp.com/topics/addictions/ultram-addiction
10. Martinez, Melissa. (n.d.). "Reasons Why Tramadol Is Prescribed." *eHow*. Available at: http://www.ehow.com/info_8197148_reasons-tramadol-prescribed.html
11. "Neuroanatomy and Physiology of the 'Brain Reward System' in Substance Abuse." (n.d.). *Institute for Behavioral Genetics, University of Colorado Boulder.* Available at: http://ibgwww.colorado.edu/cadd/a_drug/essays/essay4.htm

12. Radbruch, Lukas, Glaeske, Gerd, Grond, Stefan, Münchberg, Frank, Scherbaum, Norbert, Storz, Elisabeth, Tholen, Kathrin, Zagermann-Muncke, Petra, Zieglgänsberger, Walter, Hoffmann-Menzel, Helmut, Greve, Hendrik, Cremer-Schaeffer, Peter. (July 2013). "Topical Review on the Abuse and Misuse Potential of Tramadol and Tilidine in Germany." *Substance Abuse, Volume 34, Number 3, 1 July 2013, pp. 313-320(8)*. Available (Abstract) at: http://www.ingentaconnect.com/content/routledg/wsub20/2013/00000034/00000003/art00013
13. "Review of Abuse Risk for Tramadol." (2006-7). *Canadian Pain Society*. Available at: http://www.canadianpainsociety.ca/Tramadol/Tramadol_AbuseRisk_2006.pdf
14. Skipper, Gregory, E., Fletcher, Carol, Rocha-Judd, Rosei, & Brase, David. (2004). "Tramadol Abuse and Dependence Among Physicians." JAMA, October 20, 2004 – Vol 292, No. 15 (1818-1819). Available at: http://gregskippermd.weebly.com/uploads/7/4/7/5/74751/tramadol.jama.pdf
15. "The Consequences of Tramadol Addiction." (Nov. 2013). *Alternatives in Treatment.* Available at: http://www.alternativesintreatment.com/blog-page-posts/substances/the-potential-and-consequeses-of-tramadol-addiction/
16. "The Physical, Mental, and Emotional Impact of Tramadol." (Nov. 2013). *Alternatives in Treatment.* Available at: http://www.alternativesintreatment.com/blog-page-posts/substances/the-physicalmentalemotional-impact-of-tramadol/
17. "The Pros and Cons of Tramadol." (n.d.). *Tramadol Side Effects And Warnings.* Available at: http://www.tramadolfacts.com/pros-and-cons-of-tramadol/
18. "The Tramadol Effect." (Nov. 2013). *Alternatives in Treatment.* Available at: http://www.alternativesintreatment.com/blog-page-posts/substances/the-tramadol-effect/
19. "Tramadol." (Oct. 2013). *Medline Plus.* Available at: http://www.nlm.nih.gov/medlineplus/druginfo/meds/a695011.html#why
20. "Tramadol Abuse Signs, Symptoms and Addiction Treatment." (n.d.). *Coalition against Drug Abuse*. Available at: http://drugabuse.com/library/tramadol-abuse/
21. "Tramadol Addiction." (Jan. 2013). *Drug Addiction Treatment*. Available at: http://www.drugaddictiontreatment.com/types-of-addiction/prescription-drug-addiction/tramadol-addiction/
22. "Ultram." (Revised Jun. 2013). *Drugs.com*. Available at: http://www.drugs.com/pro/ultram.html
23. "Uses and Medical Applications of Tramadol." (2012). *Simple & Healthy Living in America.* Available at: http://www.simplelivingamerica.org/uses-and-medical-applications-of-tramadol/
24. Waters, Jo. (9 Apr. 2013). "When the 'safe option' painkiller turns out to be lethal." *Mail Online.* Available at: http://www.dailymail.co.uk/health/article-2305936/Tramadol-When-safe-option-painkiller-turns-lethal.html
25. Zabihi, Ebrahim, Hoseinzaadeh, Aateffeh, Emami, Maryam, Mardani, Mahdieh, Mahmoud, Baradaran, and Ali Akbar, Moghadamnia. (2011). "Potential for Tramadol Abuse by Patients Visiting Pharmacies in Northern Iran." *Substance Abuse: Research and Treatment 2011:5 11–15.* Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3411529/

Appendix:

Table. Drugs Abused by Physicians in Alabama and Michigan, by Category

Substance	No. of Mentions		
	Alabama	Michigan	Total
Alcohol	191	198	**389**
Opioids	190	146	**336**
Hydrocodone	86	53	**139**
Meperidine	25	10	**35**
Tramadol	23	10	**33**
Fentanyl	11	16	**27**
Codeine	11	13	**24**
Propoxyphene	10	6	**16**
Oxycodone	10	5	**15**
Morphine	8	4	**12**
Butorphanol	5	7	**12**
Pentazocine	0	9	**9**
Other	0	14	**14**
Sedatives	59	10	**69**
Stimulants	34	21	**55**
Marijuana	12	11	**23**

Figure 1:-Drugs Abused by Physicians in Alabama and Michigan, by Category(Extracted from: "Tramadol Abuse and Dependence Among Physicians.")

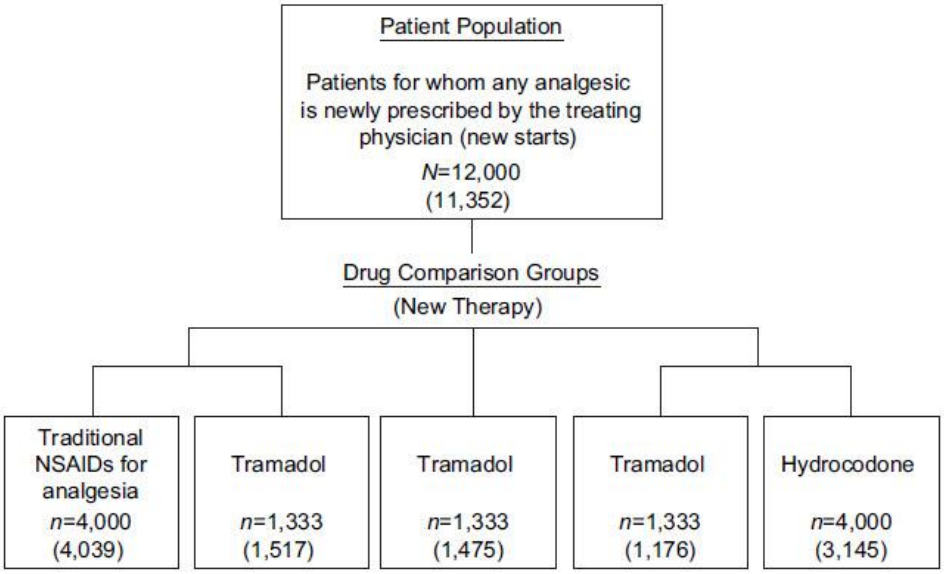

Figure 2:-Subject population, drug comparison groups. Numbers in parentheses are the actual numbers achieved vs. the target numbers.(Extracted from: "A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain.")

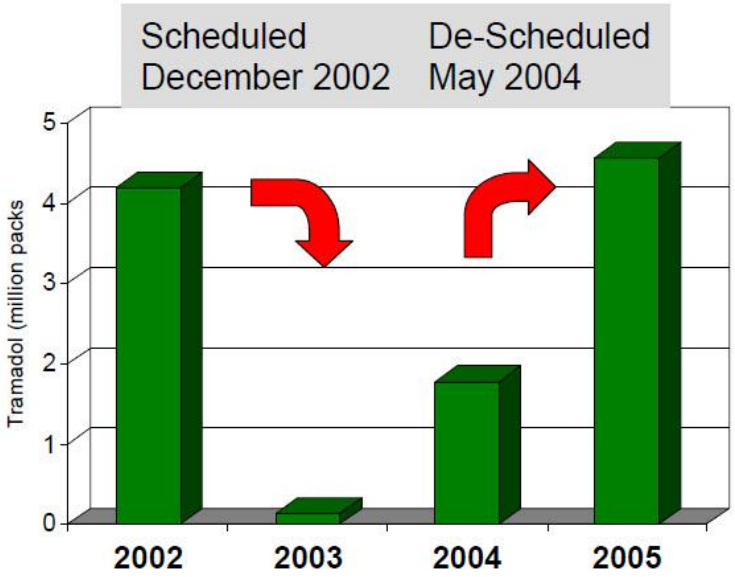

Figure 3:-Impact of Scheduling and De-scheduling of Tramadol in Egypt(Extracted from: "Review of Abuse Risk for Tramadol.")

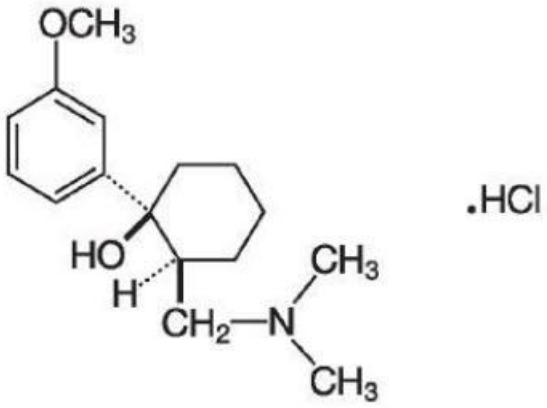

Figure 4:-Tramadol Structural Formula(Extracted from: "Ultram")

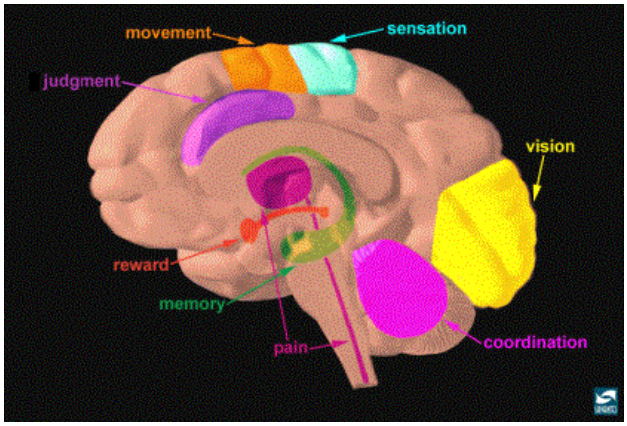

Figure 5:-Functional Areas of the Brain (Extracted from: "Neuroanatomy and Physiology of the 'Brain Reward System' in Substance Abuse.")