

# ACMD

## Advisory Council on the Misuse of Drugs

---

### **ACMD consideration of tramadol**

February 2013

# ACMD

## Advisory Council on the Misuse of Drugs

---

Chair: Professor Les Iversen CBE

Secretary: Rachel Fowler

3<sup>rd</sup> Floor Seacole Building

2 Marsham Street

London

SW1P 4DF

020 7035 0555

Email: [ACMD@homeoffice.gsi.gov.uk](mailto:ACMD@homeoffice.gsi.gov.uk)

Home Secretary

Rt Hon. Theresa May MP

Home Office

2 Marsham Street

London

SW1P 4DF

Secretary of State for Health

Rt Hon. Jeremy Hunt MP

Department of Health

79 Whitehall

London

SW1A 2NS

13 February 2013

Dear Home Secretary and Secretary of State for Health,

**Re: ACMD advice on tramadol**

I am writing to provide you both with advice from the Advisory Council on the Misuse of Drugs (ACMD) on the compound tramadol ((±)-*trans*-2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexanol). The recommendations concern both the Home Office (recommendations 1 and 2) and the Department of Health (recommendation 3).

The ACMD's review of harms associated with the non-medicinal use of tramadol was prompted by an increasing number of reports within the NHS of tramadol's misuse and harms. The ACMD's subsequent review of the evidence has caused it concern, particularly the increase in tramadol related deaths.

### *Tramadol's pharmacology, misuse and harms*

Tramadol is a synthetic analogue of the phenanthrene alkaloid codeine and is an analgesic of significant medical use for treating moderate to severe pain. Tramadol has wide ranging applications, including the treatment of fibromyalgia (chronic widespread pain), cancer pain and moderate to severe musculoskeletal pain. In a similar way to other psychoactive agents of the opioid class, it can be liable to misuse.

Tramadol has a unique dual-action pharmacological profile that increases the risk of adverse effects seen in overdose. Opioids such as tramadol exhibit weak agonist activity at opiate receptors in the brain and may contribute towards euphoria and respiratory depression. In addition, tramadol enhances serotonergic and noradrenergic systems in the brain by inhibiting their reuptake mechanisms.

Prescribing data from the NHS Business Services Authority (NHSBSA) indicate an increase in prescribing, with the number of Daily Defined Doses (England)<sup>1</sup> increasing from approximately 5.9 million in September 2005 to 11.1 million in September 2012. This may be associated with Co-Proxamol's phased withdrawal from 2005.

Data from the Office of National Statistics (ONS) for 2011 shows 154 deaths where tramadol had been mentioned on the death certificates; in 2009 there were 87 such mentions and in 2008 this figure was 83. The majority of tramadol related deaths are where it has been obtained through non-prescribed means.

### *ACMD advice*

The ACMD advises that tramadol be controlled as a class C substance under the Misuse of Drugs Act 1971 and listed in Schedule III of the Misuse of Drugs Regulations 2001, which it considers would provide the correct controls to prevent diversion and misuse.

---

<sup>1</sup> The Defined Daily Doses (DDD) is a measure of prescribing volume maintained by the World Health Organisation (WHO) based upon international prescribing behaviour. It represents the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD is not a recommended dose but an analytical unit to compare prescribing activity.

The ACMD also advises that prescribers and other healthcare professionals who come into contact with people using tramadol should be given appropriate training and support concerning its misuse and adverse effects, especially with regards to its 'dual-action'.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'Les Iversen'. The signature is written in a cursive style with a large initial 'L'.

**Professor Les Iversen FRS CBE**

## Contents

	<b>Page</b>
<b>1. Background and scope</b>	<b>6</b>
<b>2. Introduction</b>	<b>6</b>
<b>3. Pharmacology and toxicology</b>	<b>8</b>
<b>4. Dependence liability and misuse</b>	<b>10</b>
<b>5. Deaths attributed to tramadol</b>	<b>13</b>
<b>6. Conclusions and Recommendations</b>	<b>16</b>
<b>7. References</b>	<b>19</b>

## **1. Background and scope**

- 1.1. The ACMD is established under the Misuse of Drugs Act 1971 (hereafter termed the 'Act') and its purpose is to keep under review the drugs situation in the UK and provide advice to ministers. That advice may be concerned with; restricting availability, facilities and treatment (recovery), promoting co-operation between professional and community services, educating the public and promoting research.
- 1.2. This review follows concerns reported to the ACMD by an NHS Primary Care Trust (PCT) surrounding the non-medicinal use of tramadol. This includes tramadol that is illicitly obtained or prescribed legitimately but then misused. The PCT led a Controlled Drugs Local Intelligence Network, through which it had received an increasing number of reports of tramadol's misuse and harms.
- 1.3. This report examines the pharmacology of tramadol, its current non-medicinal use in the UK and the harms associated with tramadol use (medicinally and non-medicinally).

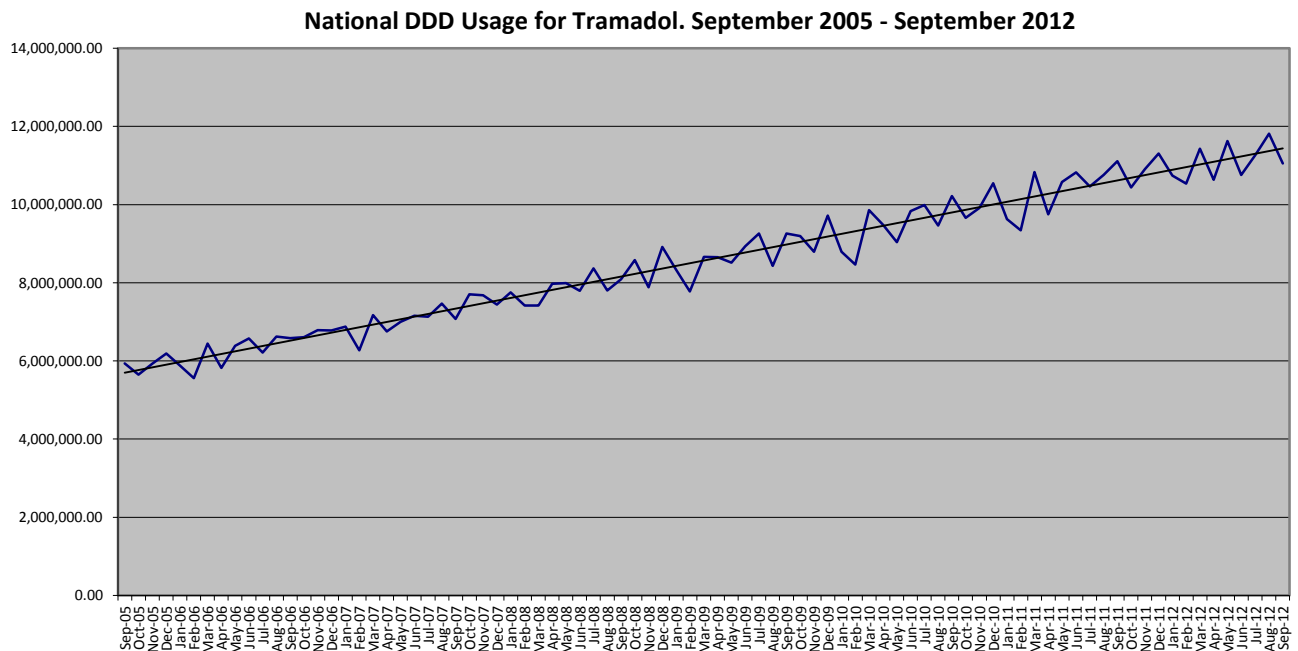
## **2. Introduction**

- 2.1. Tramadol is a synthetic opioid with effects similar to those of codeine. It is an analgesic of significant medical use and has wide ranging applications mostly in the treatment of moderate to severe pain and including the treatment of fibromyalgia (wide spread chronic pain), cancer pain and moderate to severe musculoskeletal pain.
- 2.2. Tramadol is classified as an "other opioid" under the World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) classification system and sits on step two of the WHO analgesic ladder with opiates such as codeine and dihydrocodeine. It is regarded as equipotent to these two opiates.
- 2.3. Tramadol has other trade names such as Zydol®, Zamadol® and Marol®.
- 2.4. The ACMD understands that tramadol is widely available on-line and easily obtainable without prescription. Current medicines legislation does not prohibit the importation of a medicine, provided it is for personal use and not for onward supply.
- 2.5. The side effects of tramadol can include hallucinations, agitation, fever, overactive reflexes, nausea, vomiting, loss of coordination, fainting and elevated heart rate.

2.6. Figures for England indicate that Defined Daily Doses (DDD)<sup>2</sup> have increased from approximately 5.9 million in September 2005 to 11.1 million in September 2012 (Figure 1).

2.7. Compared to other analogous compounds e.g. dihydrocodeine it would appear an anomaly that tramadol is an opioid outside the Misuse of Drugs Act 1971. The ACMD notes the level of licit prescribing of tramadol as suggested by recent data (Figure 1).

2.8. The Medicines and Healthcare products Regulatory Agency (MHRA) has received 67 referrals regarding or linked to tramadol (some referrals have included other medicines as well). As a result, the MHRA has launched a number of investigations, some of which were linked to the counterfeiting of tramadol.



**Figure 1.** National DDD usage for tramadol (September 2005 to September 2012).

<sup>2</sup> The Defined Daily Doses (DDD) is a measure of prescribing volume maintained by the World Health Organisation (WHO) based upon international prescribing behaviour. It represents the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD is not a recommended dose but an analytical unit to compare prescribing activity

## ***International Perspective***

- 2.9. The legal status of tramadol differs internationally, from being available over the counter in Kuwait and Thailand to being a controlled (Schedule 4) prescription drug in Australia since 2001. In Sweden it has been controlled in the same manner as dextropropoxyphene and codeine since 2008, and in Norway, Ireland and Germany it is a prescription only medicine. The ACMD understands that in the USA tramadol is controlled under some states' laws (Schedule 4) e.g., Arkansas and Kentucky.

## **3. Pharmacology and Toxicology**

### ***Pharmacology***

- 3.1. Tramadol – ( $\pm$ )-*trans*-2-((dimethylamino)methyl)-1-(3-methoxyphenyl)cyclohexanol – is a synthetic opioid with effects similar to those of codeine. It is an analgesic with weak agonist activity at  $\mu$ -opioid receptors in the brain ( $K_i = 2400$  nM; Gillen *et al.*, 2000). The affinity of tramadol for the  $\mu$ -opioid receptor is only 1/6000 of that of morphine although its selectivity for this sub-type of receptor is greater than that of morphine. Its analgesic activity is also probably contributed to by monoaminergic activity resulting from inhibition of re-uptake of both noradrenaline and serotonin and from some agonist activity at  $\alpha_2$  adrenergic receptors. The fact that, in contrast to other opioids, the analgesic action of tramadol is only partially inhibited by the opioid antagonist naloxone lends support to the view that these other actions play a role in its analgesic activity. However, Duke *et al.* (2011) found that subjects trained to discriminate the subjective effects of an opiate (dihydromorphine) from those caused by a stimulant (methylphenidate) recognised tramadol as an opiate drug. Gillen *et al.* (2000) reported that the primary *O*-desmethylated metabolite of tramadol interacts potently with the cloned human  $\mu$ -opioid receptor ( $K_i = 3.4$  nM), making it more than 700 times more potent than the parent compound. This suggests that the *O*-demethylated metabolite may account for most of tramadol's opiate-mediated analgesic activity (Gillen *et al.*, 2000)<sup>3</sup>. A range of other pharmacological actions have been attributed to tramadol. In particular, it has been reported as having actions on various G-protein coupled receptors (GPCRs) and on ion channels. There are specific reports of actions as an NMDA receptor antagonist, a 5-HT<sub>2C</sub> receptor antagonist, and an antagonist at both nicotinic and muscarinic acetylcholine receptors (Minami *et al.*, 2007). The significance of these actions in the therapeutic use of the drug or in the development of adverse reactions is not clear.

---

<sup>3</sup> The ACMD provided advice on the misuse and harms of *O*-desmethyltramadol in 2012. The legislative process for control of the substance under the Misuse of Drugs Act 1971 is underway.



- 3.2. Tramadol is a racemic mixture<sup>4</sup>, the parent racemate being more potent as an analgesic than either of its enantiomers although the (+) enantiomer does bind to the  $\mu$ -opioid receptor and does inhibit the re-uptake of serotonin. The (-) enantiomer inhibits the re-uptake of noradrenaline and stimulates  $\alpha_2$  receptors (Raffa, 2008).
- 3.3. Tramadol undergoes liver metabolism and is excreted via the kidney. The elimination half-life is 6 hours for tramadol and 7.5 hours for its active metabolite. The analgesic effect begins within about an hour of oral dosing, peaks at 2-3 hours and lasts for about 6 hours. The maximum recommended daily dose by mouth is 400mg (Dayer, *et al.*, 1997).
- 3.4. Tramadol is about as effective as morphine in the relief of mild to moderate pain but less effective in the treatment of severe or chronic pain. Reported subjective effects in therapeutic use include euphoria and other reported effects include dizziness, headache, agitation, nausea, vomiting and seizures. It appears to cause less respiratory depression than other opioids, but this is still a risk with large doses of tramadol, either therapeutically or in overdose. Patients with renal impairment and extensive CYP2D6 metabolisers are at enhanced risk of toxicity (Stamer, *et al.*, 2008).
- 3.5. In summary, although tramadol has a complex pharmacology, its analgesic action results mainly from its agonist effects at opioid receptors with an additional contribution from the monoaminergic activity due to its inhibition of the re-uptake of serotonin and noradrenaline. This dual mechanism increases the potential for adverse effects, particularly in overdose, and has led to debates about whether or not tramadol should be classified as an opioid and whether its toxicity, including misuse and dependency potential, should be regarded as being different from that of other opioids (Raffa, 2008; Epstein, *et al.*, 2006).

### **Toxicology**

- 3.6. Tramadol overdose results in drowsiness, constricted (small) pupils, agitation, tachycardia (rapid heartbeat), hypertension (high blood pressure), and nausea, vomiting and sweating. Seizures are more common with tramadol overdose than with other opioids and occur in up to 15% of cases. In severe poisoning coma, seizures and hypotension (low blood pressure) can occur; respiratory depression is less common than with other opioids unless the individual has taken other central nervous system depressants.

---

<sup>4</sup> A racemic mixture is one that comprises of left- and right-handed enantiomers (i.e. mirror images) in equal amounts.

- 3.7. Due to the fact that tramadol inhibits serotonin re-uptake, tramadol overdose can cause serotonin syndrome. This can be potentially fatal with severe serotonin syndrome being characterised by hyperpyrexia (very high body temperature) associated with secondary complications including rhabdomyolysis (breakdown of skeletal muscle), disseminated intravascular coagulation (formation of blood clots) and acute kidney injury. This syndrome is more likely to occur with co-administration of another drug that increases serotonin activity such as certain antidepressants (e.g. monoamine oxidase inhibitors, SSRIs (Selective serotonin re-uptake inhibitors)) and stimulant recreational drugs with serotonergic activity (e.g. MDMA (ecstasy), amphetamines, cathinones (e.g. mephedrone)).
- 3.8. The fact that only the opioid effects of tramadol are reversible with naloxone makes this drug more likely to cause harm than other opioids especially when combined with other monoamine-active drugs as noted above.

#### **4. Dependence liability and misuse**

- 4.1. One view is that 'tramadol has pharmacodynamic and pharmacokinetic properties that are highly unlikely to lead to dependence' (Dayer, *et al.*, 1997) and in another paper it is stated that 'while abuse of tramadol may occur, several large studies have demonstrated that the incidence of abuse is rather low, about one case per 100,000 patients' (Reeves and Burke, 2008). However, some authors have suggested incidence of abuse or dependence as high as 6.9/1000 in some cohorts of users (Knisely, *et al.*, 2002).
- 4.2. Tramadol has been reported as having a lower potential for dependence compared to morphine and animal studies have demonstrated a lower abuse potential than codeine and pentazocine (Epstein, *et al.*, 2006). The Summary of Product Characteristics for Zydol® capsules, which contain the active ingredient tramadol hydrochloride, also highlight that they have a "low dependence potential" (Martindale, The Extra Pharmacopoeia, 2009). In 2006 a WHO expert committee on drug dependence reviewed tramadol and concluded that, despite an increase in its use, it continued to show a low level of misuse and that there was not sufficient evidence to justify a further review (WHO, 2006).
- 4.3. Reports of dependence and misuse in the UK through the National Drug Treatment Monitoring System (NDTMS) highlighted just over 300 cases since 2004 of tramadol being reported as a primary drug in England with 200 cases reporting tramadol as a secondary drug. Although it is difficult to give an accurate figure of how many individuals this relates to (multiple episodes can be recorded for one individual presenting to treatment) it has been estimated that it relates to about 200 individuals (Donmall, 2010).

- 4.4. Where physical dependence to tramadol develops the withdrawal syndrome (Barsotti, *et al.*, 2003) can be severe with symptoms typical of opiate withdrawal sometimes accompanied by atypical symptoms including seizures. The latter are probably related to the effects of monoamines.
- 4.5. It is relevant to note that the somewhat more potent but related drug tapentadol which has recently been licensed for clinical use is a Schedule II drug. A research report by Terault, *et al.* (2007) examined gender and non-medical use of a number of prescription opioids in the USA (Table 1).

Opioid	Total sample % (n) n = 55 023	Past-year non-medical use of prescription opioids % (n)			P*
		Women and men % (n) n = 4125	Women % (n) n = 2004	Men % (n) n = 2125	
Darvocet, Darvon, Tylenol with codeine, propoxyphene/SK65	8.4 (5134)	62.4 (2406)	60.7 (1162)	64.0 (1244)	0.23
Vicodin, hydrocodone Lortab or Lorcet	7.1 (5124)	65.4 (2759)	63.2 (1262)	67.5 (1497)	0.12
Percocet, Percodan or Tylox	4.5 (2844)	38.5 (1480)	30.7 (628)	45.6 (852)	<0.0001
Codeine, Phenaphen	3.1 (2137)	26.7 (1217)	22.0 (529)	31.0 (678)	0.0002
Oxycontin	1.2 (1098)	15.5 (749)	11.9 (296)	18.8 (453)	0.0002
Demerol	1.2 (753)	11.2 (422)	8.0 (184)	14.1 (238)	0.0006
Morphine	0.9 (773)	9.3 (487)	6.9 (190)	11.6 (297)	0.0003
Methadone	0.5 (418)	5.4 (280)	4.1 (123)	6.7 (157)	0.02
Ultram, tramadol	0.5 (373)	5.6 (251)	6.8 (127)	4.5 (124)	0.09
Dilaudid	0.4 (160)	2.24 (72)	1.6 (29)	2.8 (43)	0.14
Stadol, Talacen, Talwin, TalwinNX	0.3 (127)	1.5 (63)	0.9 (29)	2.0 (34)	0.10

Results are reported as unweighted n and weighted percentages using SUDAAN, \*P-value is for  $\chi^2$ .

**Table 1.** Lifetime non-medical use of individual opioids among the total sample, and among those with past-year non-medical use of prescription opioids, stratified by gender.

- 4.6. Table 1 shows that of the total sample of 55023 individuals, 373 or 0.5% had reported lifetime non-medical use of tramadol. Past year use demonstrates high prevalence rates for the stronger opioids also with Vicodin® (hydrocodone and paracetamol) and Percocet® (oxycodone and paracetamol) at 65.4% and 38.5% respectively, compared to 5.6% for Tramadol.
- 4.7. The website EROWID (online user forum) provides 221 user reports associated with the non-medical use of tramadol<sup>5</sup>. The reports support the assumption that tramadol is used as a non-medical agent by users for its psychoactive qualities with a variety of 'positive' and 'negative' effects reported by users.
- 4.8. The 2011 Street Drug Trends survey has also indicated that there has been a rise in tramadol use in the last year in 16 of the 20 areas investigated in the UK (Daley and Simonson, 2011).

<sup>5</sup> Accessed on 7<sup>th</sup> December 2012

4.9. The ACMD is not aware of academic literature that investigates the breakdown of how individuals' access tramadol supplies, although tramadol remains widely available on prescription. Tramadol is widely available on the internet without prescription. The ACMD considers that the diversion of licit or prescription supplies would be a route that some individuals use and is aware of some case study reports from the South West of England that support this.

4.10. The ACMD is not aware of academic literature in the UK that has investigated the societal harms associated with tramadol misuse. Tramadol has been implicated as a drug that has "fuelled a lucrative criminal economy of illicit drugs" in the Occupied Palestinian Territories (Gaza) with its associated loss of tangibles for the individuals involved (there were 591 tramadol related arrests in 2009 in Occupied Palestinian Territories (Gaza) (Progler, 2010). However, it would be difficult to generalise these to the UK considering the difference between the two territories. The ACMD is mindful that tramadol dependence has been reported in the UK from data provided by the National Drug Treatment Monitoring System (NDTMS) database (see paragraph 4.3) and understand the impact opioid dependence can have on users and affected others.

4.11. The Medicines, Healthcare Products Regulatory Agency (MHRA) monitors adverse effects through the yellow card system. Information from their drug analysis print for tramadol from January 1983 (first recorded adverse effects to the MHRA) to 5<sup>th</sup> January 2011 shows :

- 6073 'reactions' to tramadol with 60 fatalities;
- the most common system organ class for an adverse reaction was 'nervous system disorders' (22.4%) with 'dizziness' the most common individual reaction in this group;
- the top three categories for fatalities adverse reaction were, injuries (22%), general disorders (20%) and respiratory disorders (18%);
- under substance-related disorders the following number of adverse effects have been reported:

Alcohol withdrawal syndrome: 1	Drug dependence: 22
Dependence: 27	Nicotine dependence: 1
Drug abuse: 5	Withdrawal syndrome: 168

4.12. The accuracy of this data depends on accurate reporting and recognition of symptoms from the reporter. Numbers above could be higher as many adverse effects may go unreported through the yellow card system. Nevertheless, through the MHRA, dependence and withdrawal symptoms have been reported as being associated with tramadol.

## 5. Deaths attributed to tramadol

5.1. Two reports on the number of deaths where selected substances were mentioned on death certificates in England and Wales also highlights the role of tramadol in drug related deaths.

5.2. Tramadol has been mentioned in a number of deaths reported to the National Programme of Substance Abuse Deaths (np-SAD). Table 2 highlights an increasing trend since 1998 when only two mentions of tramadol were noted, with 123 mentions in 2009.

Year	Number of mentions of tramadol	Deaths where tramadol was implicated	% of implicated deaths where tramadol was the "sole agent" (number)	% of implicated deaths where tramadol was NOT prescribed or "not known"(number)
1998	2	2	50 (1)	0 (0)
1999	9	12	8 (1)	33 (4)
2000	9	10	30 (3)	70 (7)
2001	29	33	15 (5)	58 (19)
2002	19	19	21 (4)	53 (10)
2003	38	37	22 (8)	41 (15)
2004	55	45	36 (16)	67 (30)
2005	61	53	34 (18)	62 (33)
2006	85	76	25 (19)	68 (52)
2007	96	82	17 (14)	62 (51)
2008	97	80	21 (17)	61 (49)
2009	138	111	11 (12)	64 (59)
2010	133	109	21 (23)	63 (58)

**Table 2:** Number of: a) "mentions" of tramadol in deaths b) deaths where tramadol has been implicated c) % of deaths where tramadol was the sole agent and d) % of deaths where tramadol was not prescribed or the route of supply was "not known" reported to the np-SAD by the end of June 2012.

5.3. The information provided by np-SAD also shows:

- a prominent diversion problem with up to 64% of deaths (2009) where tramadol has been implicated coming from non-prescribed routes or where the source was unknown; and,
- a trend towards poly-drug use with only 17% of tramadol implicated deaths in 2007 involving tramadol as the sole agent.

Drug	2006	2007	2008	2009	2010	2011
Total mentions: All deaths from drug-related poisoning:						
Methadone	241	325	378	408	355	486
All benzodiazepines	177	207	230	261	307	293
All anti-depressants	336	335	381	405	381	393
Paracetamol (including combination products) <sup>6</sup>	309	242	260	255	199	207
Codeine	60	60	70	90	91	* <sup>7</sup>
Dihydrocodeine	96	85	79	99	90	*
Tramadol	81	79	83	87	132	154

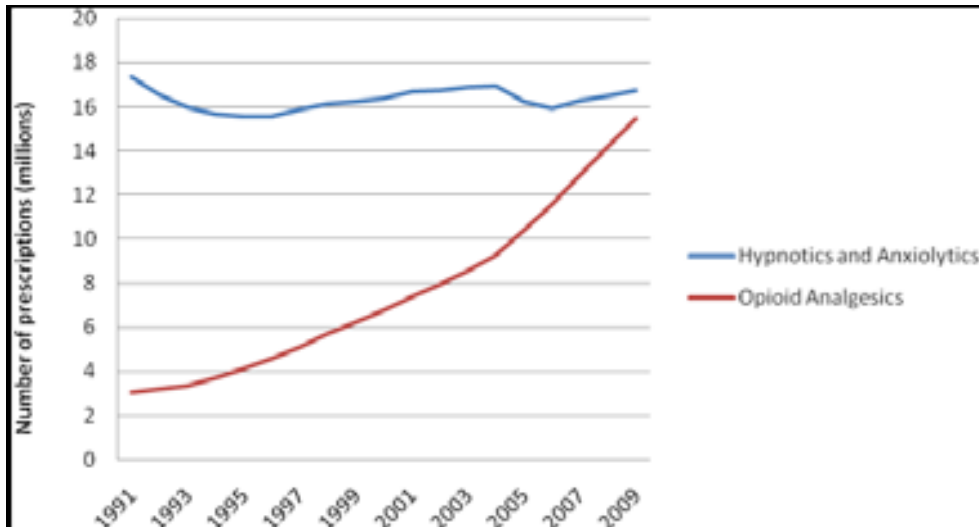
**Table 3:** Number of deaths where selected substances were mentioned on death certificates. Deaths related to drug poisoning in England and Wales 2006-10 (ONS).

5.4. According to data from the ONS, the number of deaths involving tramadol have also been steadily increasing since 1993 (when ONS records began), with deaths showing a marked rise from 87 in 2009 to 154 in 2011 (an increase of 77 per cent) (Table 3).

<sup>6</sup> Dextropropoxyphene is very rarely ingested except in combination with paracetamol, therefore figures include dextropropoxyphene mentioned without paracetamol.

<sup>7</sup> Notes (ONS) Specific rules were adopted for dealing with compound analgesics which contain relatively small quantities of drugs listed under the Misuse of Drugs Act, the major ones being dextropropoxyphene, dihydrocodeine and codeine. Where these drugs are mentioned on a death record, they have been excluded from the drug misuse indicator if they are part of a compound analgesic (such as co-proxamol, co-dydramol or co-codamol) or cold remedy.

- 5.5. Table 3 shows that deaths where tramadol was mentioned on the death certificate have increased (apart from a small decrease in 2007). It is important to note this increase has occurred at a time when there has been a large increase in prescribing. Table 3 also highlights the role of other drugs in drug-related poisonings.
- 5.6. The 2009 Drug-related deaths in the UK report published by the np-SAD mentions that the proportion of deaths involving tramadol rose from 2.2% in 2004 to 3.6% in 2006 and has since remained stable (Ghodse, *et al.*, 2009).
- 5.7. A review of deaths related to analgesic and cough suppressant-opioids in England and Wales between 1996 and 2002 by Schifano *et al.* in 2006 illustrated that codeine and dihydrocodeine were reported in about 28% of cases with a smaller number related to other analgesics (including tramadol) (Office National Statistics, 2008).
- 5.8. When interpreting these figures it should be noted that the prescribing of tramadol has also increased since the phased withdrawal of Co-Proxamol between January 2005 and December 2007. Figures for England indicate that DDD have increased from approximately 5.9 million in September 2005 to 11.1 million in September 2012 (Figure 1).
- 5.9. The phased withdrawal of co-proxamol in 2005 may have impacted on tramadol prescribing levels as prescribers sought alternative analgesia (see Figure 2). However, it should be noted that the number of prescriptions for opioid analgesics dispensed in England have also increased significantly over the same period (Figure 1). A report from the National Treatment Agency (NTA) in 2011 illustrates that from 1991 to 2009 opioid analgesic medication dispensed in England has increased by over fivefold (NTA, 2011) (Figure 2). Therefore, it is not clear whether this is a general trend or whether the phased withdrawal has had a significant impact on prescribing levels. Nevertheless, it is clear that levels of prescribing have increased as have drug related deaths where tramadol has been mentioned.



**Figure 2:** trends in prescribing of opioid analgesics hypnotics and anxiolytics (by number of prescriptions (millions) and quantity in the number of items dispensed (1991-2009) (NTA, 2011).

## 6. Conclusions and Recommendations

- 6.1. Tramadol is a widely prescribed analgesic of significant medical use for the treatment of moderate to severe pain. In a similar way to other psychoactive agents of the opioid class, it is liable to misuse.
- 6.2. Tramadol's unique dual-action pharmacological profile increases the risk of adverse effects, particularly in overdose. The symptoms of tramadol overdose include rapid heart beat, high blood pressure, vomiting and seizures. Tramadol overdose can cause serotonin syndrome, which is potentially fatal. Treatment of tramadol overdose with naloxone only reverses the opioid effects, therefore, it is more likely to cause harm than other opioids, especially when combined with other monoamine-active drugs e.g., ecstasy.
- 6.3. The NDTMS highlighted just over 300 cases since 2004 of tramadol being reported as a primary drug of use in England, with 200 cases reporting tramadol as a secondary drug. It has been estimated that it relates to about 200 individuals. The 2011 Street Drug Trends survey has also indicated that there has been a rise in tramadol use in the last year in 16 of the 20 areas investigated in the UK.
- 6.4. Data from the ONS for 2011 shows 154 deaths where tramadol had been mentioned on the death certificates; in 2009 there were 87 such mentions and in 2008 this figure was 83. The majority of tramadol related deaths are where it has been obtained through non-prescribed means.



- 6.5. The ACMD is not aware of academic literature that investigates the breakdown of how individuals' access tramadol supplies, although tramadol remains widely available on prescription and on the internet without prescription. The ACMD considers that the diversion of licit or prescription supplies would be a route that some individuals use.
- 6.6. The ACMD are not aware of academic literature in the UK that has investigated the societal harms associated with tramadol misuse. However, tramadol dependence has been reported in the UK from data provided by the NDTMS and it is important to recognise the impact opioid dependence can have on users and society.

### **Recommendation 1**

**The ACMD considers the harms associated with tramadol are commensurate with other Class C drugs and recommends that it is controlled under the Misuse of Drugs Act 1971 as a Class C substance.**

- 6.7. The ACMD is aware that tramadol is widely available on the internet without prescription. There is some evidence to suggest diversion of prescription supplies destined for misuse, however, the ACMD does not have evidence to quantify this (see paragraph 4.10).
- 6.8. The ACMD considers that to provide an appropriate level of control, both due to the complex pharmacology of tramadol making this drug more likely to cause harm than other equipotent opioids and to enable additional monitoring particularly around private prescribing, the most appropriate Schedule for tramadol would be Schedule III.
- 6.9. It is important to note that in the absence of evidence from clinical practice, the ACMD is unclear whether the prescription requirements associated with Schedule III could present further burden for prescribers. Should the Home Office consider implementing the above recommendation, the ACMD would consider it prudent for it to consult with health and social care practitioners on the impact of Schedule III (Regulation 15) requirements to ensure any change is proportionate to the harms and risk of diversion outlined by the ACMD in this report.

### **Recommendation 2**

**Tramadol be scheduled as a Schedule III drug under the Misuse of Drugs Regulations 2001 (as amended).**

- 6.10. The DDD for tramadol of 11.1 million (September 2012, up from 5.9 million in September 2005), reflects the level of prescribing by practitioners. As with all medicines that are scheduled under the Misuse of Drugs Regulations, irrespective of scheduling category it is required that prescribers are provided with adequate training and information to ensure the safe use of the medicine given. The judicious prescribing of tramadol is essential to its safe use.
- 6.11. Given the widespread prescribing of tramadol it is important that there is appropriate information and training provided to prescribers. The raising of awareness among prescribers of the potential harms associated with the misuse of tramadol would assist in addressing issues such as the improper prescribing of tramadol (as highlighted by the North of Tyne Intelligence Network) and the risks of diversion.
- 6.12. The misuse of tramadol, from whatever source, presents potential physical harms to the user. There are also potential social harms around the impact that opioid dependence can have on those other than the user.

### **Recommendation 3**

**The ACMD recommends that prescribers and other healthcare professionals who prescribe, or come into contact with people who use tramadol should be given appropriate training and support concerning its misuse and adverse effects, especially with regards to its 'dual-action'.**

**This training, together with classification (see recommendation 1), will support prescribers and healthcare professionals in reducing harm associated with the misuse or inappropriate prescribing of tramadol.**

## References

Addiction to Medicine; An investigation into the configuration and commissioning of treatment services to support those who develop problems with prescription only or over-the-counter medicine, National Treatment Agency (May 2011).

Barsoti CE, Mycyk MB, Reyes J. Withdrawal syndrome from tramadol hydrochloride. *American Journal of Emergency Medicine* (2003) 21 (1) 87-88

Daley and Simonson, Street drug trends survey 2011

Dayer P, Desmeules J, & Collart L. Pharmacology of tramadol. *Drugs* (1997) 53 18-24

Duke A N, Biqelow G E, Lanier R K, Strain E C. (2011) Discriminative stimulus effects of tramadol in humans. *Journal of Pharmacology and Experimental Therapeutics* Jul 2011;338(1):255-6E2p. Epub 2011 Apr 5

Epstein D H, Preston K L, Jasinski R. (2006) Abuse liability behavioural pharmacology, and physical dependence potential of opioids in humans and laboratory animals: lessons from tramadol. *Biological Psychology* 2006 Jul; 73 (1): 90-9E

Ghodse H, Corkery J, Oyefeso A, Schifano F, Ahmed K, Naidoo V. (2009) Drug-related deaths in the UK. Annual npSAD Report 2009.

Gillen C, Haurand M, Kobelt DJ, Wnendt, S (2000) Affinity, potency and efficacy of tramadol and its metabolites at the cloned human  $\mu$ -opioid receptor. *Naunyn-Schmiedeberg's, Archives of Pharmacology*, 362:116-121

Knisely J, Campbell ED, Dawson KS, Schnoll SH. Tramadol post-marketing surveillance in health care professionals. *Drug and Alcohol Dependence*. (2002) 68: 1; 15-22.

Martindale: The Extra Pharmacopoeia (2009) 36; 131-132.

Medicines and Healthcare Regulatory Authority (MHRA) Tramadol Drug Analysis Print (DAP). (accessed at <http://www.mhra.gov.uk> on 21/02/2010)

Minami K, Uezono Y, Ueta Y. Pharmacological aspects of the effects of tramadol on G-protein coupled receptors *Journal of Pharmacological Sciences* (2007) 103 253-260

Office for National Statistics (ONS). Report: Deaths related to drug poisoning in England and Wales, 2003-07. (2008)

Office for National Statistics (ONS). Report: Deaths related to drug poisoning in England and Wales, 2010. (2011)

Personal communication with Michael Donmall, Reader in Addictions Research and Director of the National Drug Evidence Centre, University of Manchester on 21/10/2010.

Personal communication with John Corkery, St Georges, University of London 7/10/2010

Personal communication with Louisa Felgate, Substance Misuse Specialist, Harbour Drug and Alcohol Service, Plymouth on 10/11/2010.

Personal communication with Carol Webb, controlled drug technician, NHS Plymouth Medicines Management Team on 10/11/2010.

Progler, Y. Drug addiction in Gaza and the illicit trafficking of tramadol. *J Res Med Sci.* 2010 15(3):185-8.

Raffa, RB. Basic pharmacology relevant to drug abuse assessment: tramadol as example. *Journal of Clinical Pharmacy & Therapeutics* (2008) 33 101-108

Reeves RR, & Burke R S. Tramadol: basic pharmacology and emerging concepts *Drugs of Today* (2008) 44 827-836

Schifano F *et al.* Review of deaths related to analgesic and cough suppressant-opioids; England and Wales 1996-2002. (2006)

Stamer U, Stuber F, Muders T, Musshoff F. Respiratory Depression with Tramadol in a Patient with Renal Impairment and CYP2D6 Gene Duplication. *Anesthesia & Analgesia* 2008; 107: 926–929.

Tetrault JM, *et al.* Gender and non-medical use of prescription opioids: results from a national US survey. *Addiction.* (2007) 103: 258-268.

The Vaults of Erowid website (accessed at <http://www.erowid.org/pharms/tramadol/tramadol.shtml> on 15/02/2010)

World Health Organisation (WHO). WHO Technical Report Series 942: WHO Expert Committee on Drug Dependence. 34<sup>th</sup> Report. (2006)

Zydol® 50mg Capsules Summary of Product Characteristics (SPC) (accessed <http://www.medicines.org.uk/emc/medicine/16371/SPC/Zydol+50mg+Capsules/> on 01/03/2011)