Prescriptions of gabapentinoids – what should we learn from the insights of Malcolm Lader?

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addictovigilance.fr
le site de l'association française des centres d'addictovigilance

Hôpitaux de Toulouse

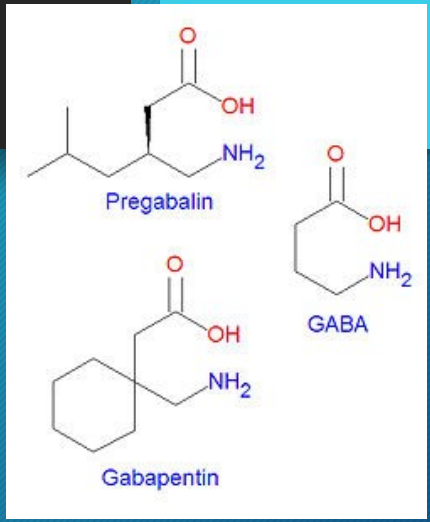
No conflict of interest

Funding from the French Medicine Agency (ANSM) for the French Addictovigilance system (annual funding)

Master research scholarship supported by the Toulouse University Hospital for medical residents (Master in clinical epidemiology)

« Gabapentinoids »: gabapentin and pregabalin

- Gabapentinoids
  - Not directly acting on GABA receptor
  - Acting on voltage-gated calcium channels
- Gabapentin "old" drug 1st approval in France
  - Antiepileptic drug and zoster pain
- Pregabalin 1st approved in Europe in 2004
  - Antiepileptic
  - Neuropathic pain
  - General anxiety disorder



Special safety issue

Abuse potential: The abuse potential of pregabalin was studied in a separate study (098) versus diazepam and placebo. Pregabalin did not have the profile of a prototypic drug of abuse when compared with diazepam.

Withdrawal and rebound phenomena: No proper studies were performed to assess withdrawal and rebound phenomena in particular in patients with epilepsy. As a consequence, the summary of product characteristics states that in accordance with current clinical practice, if pregabalin has to be discontinued either in neuropathic pain or epilepsy, it is recommended this should be done gradually over a minimum of 1 week.

Initially presented with a negligible abuse potential, whereas their pharmacodynamics effects are similar to that observed with benzodiazepines : sedative, anxiolytic, anticonvulsant ⇒ « psychoactive drugs »

Focus on Pregabalin

Special safety issue

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- First assessment by the EMA

The lack of any dependence or abuse signal from the gabapentin post-marketing database provides confidence that pregabalin would similarly not be associated with abuse or dependence.

For thoroughness, the pregabalin database has been examined extensively for any signs of dependence potential in accordance with established indicators.

- …. First case reports of abuse in 2006!!!
  - Germany, Italy, Turkey
  - First signal of abuse and dependence : 2010

The story begins

- Sporadic cases of abuse with gabapentin in the early 2000s
- 1st report of pregabalin abuse in France in 2011
- Pregabalin identified as NPS in 2010 by the EMCDDA (from Sweden, UK and Finland)

Eur J Clin Pharmacol (2010) 66:947–953
DOI 10.1007/s00228-010-0853-y

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

A signal for an abuse liability for pregabalin—results from the Swedish spontaneous adverse drug reaction reporting system

Sofie Schwan · Anders Sundström · Elisabet Stjernberg · Ebba Hallberg · Pär Hallberg

CNS Drugs (2016) 30:647–654
DOI 10.1007/s40263-016-0359-y

ORIGINAL RESEARCH ARTICLE

A Decade of Gabapentinoid Misuse: An Analysis of the European Medicines Agency's 'Suspected Adverse Drug Reactions' Database

Stefania Chiappini[1] · Fabrizio Schifano[2]

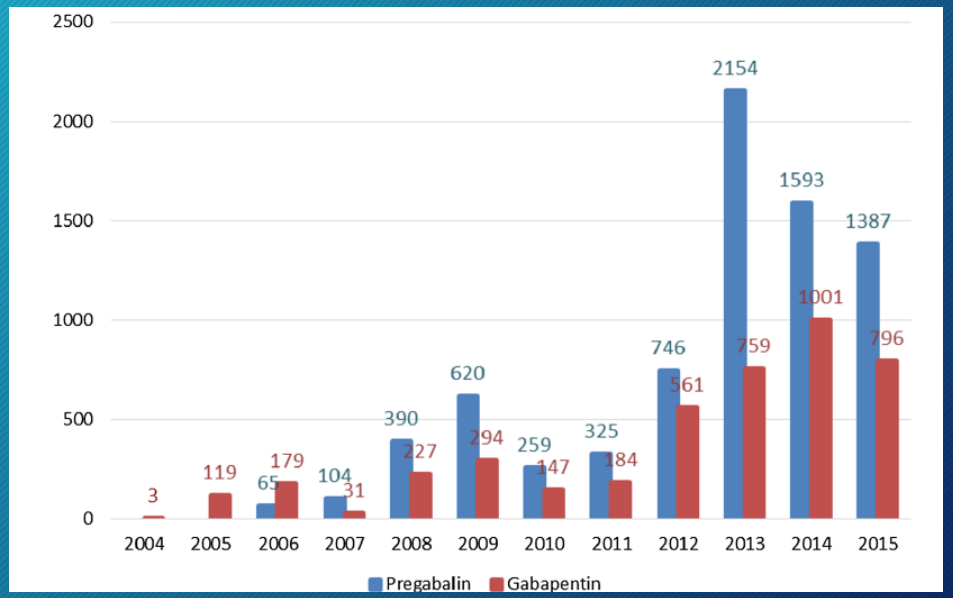
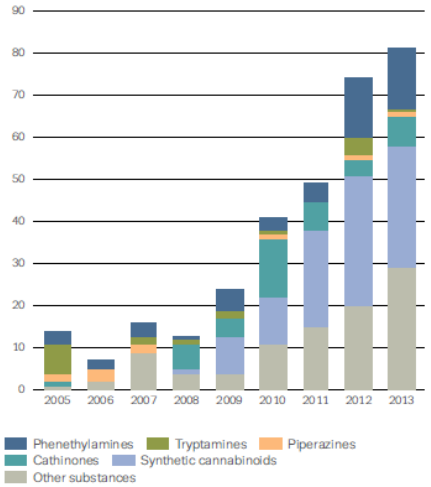


FIGURE 1.13

Number and main groups of new psychoactive substances notified to the EU Early Warning System, 2005–13



controls, products are often mislabelled, for example as 'research chemicals' or 'plant food' with disclaimers that state the product is not intended for human consumption.

During 2013, 81 new psychoactive substances were notified by the Member States for the first time through the EU Early Warning System (Figure 1.13). Twenty-nine of these substances were synthetic cannabinoids and another 30 compounds did not conform to the readily recognised chemical groups (including plants and medicines). There were also 13 new substituted phenethylamines reported, seven synthetic cathinones, a tryptamine and a piperazine.

During 2013, 81 new psychoactive substances were notified by the Member States for the first time through the EU Early Warning System

Assessing the risk of new drugs

European-level risk assessments were undertaken on 4-methylamphetamine (in 2012) and 5-(2-aminopropyl) indole (in 2013), in response to emerging evidence of harms that included over 20 fatalities associated with each substance over a short period of time. Both of these substances were subjected to control measures throughout Europe. Four new psychoactive substances (25I-NBOMe, AH-7921, MDPV, methoxetamine) were risk-assessed in April 2014.

25I-NBOMe is a substituted phenethylamine and a potent full agonist of the serotonin 5-HT2A
appears to have hallucinogenic effec
available on the EU drug market sinc
Severe toxicity associated with its us
in four Member States, including one
substance was detected.

AH-7921 is a synthetic opioid, which
the European Union since at least Ju
cases, it has been seized in small qu
This opioid has been detected in six
and fifteen deaths in Sweden, the Un
Norway.

MDPV is a synthetic cathinone deriva
pyrovalerone. MDPV has been preser
market since at least November 200
detected in up to 107 non-fatal intox
deaths, particularly in Finland and th
There are some indications that it ha
or synthetic version of cocaine, and i
in tablets resembling 'ecstasy'.

Methoxetamine is an arylcyclohexyla
to ketamine, and has been available on the EU drug market since at least September 2010. Multi-kilogram quantities of the substance in powder form have been seized. Twenty deaths and 110 non-fatal intoxications associated with the substance have been reported.

New psychoactive substances can appear on the market either under the guise of a controlled drug, or as an alternative to a controlled drug. For example, 4-methylamphetamine was sold directly on the illicit drug market as amphetamine, methoxetamine is marketed as a legal alternative to ketamine and 25I-NBOMe is sold as a 'legal' alternative to LSD (lysergic acid diethylamide).

More medicines detected

A growing number of new drugs that are detected on the drug market have legitimate use as medicines. Sometimes they are sold as medicines, in other cases they are sold clandestinely as illicit drugs such as heroin, or they may be sold as 'legal highs', 'research chemicals', and even as 'food supplements'. Recent examples, all reportedly injected by opioid users include pregabalin used for treating neuropathic pain, epilepsy and generalised anxiety; tropicamide, used during eye examinations to dilate the pupils; and carfentanil, an opioid used to tranquillise large animals.

European Drug Report 2014
Trends and developments

Signal of pregabalin abuse in Eudravigilance in 2013 (number of reports higher than expected, mainly from Nordic countries)

Gabapentinoids abuse in France ?

- First report of pregabalin recreational use in 2011
- Addictovigilance monitoring : increasing number of falsified prescriptions and increasing reporting in methadone patients seen in addiction care centers
- Few cases for gabapentin

‘Explode’ in 2019

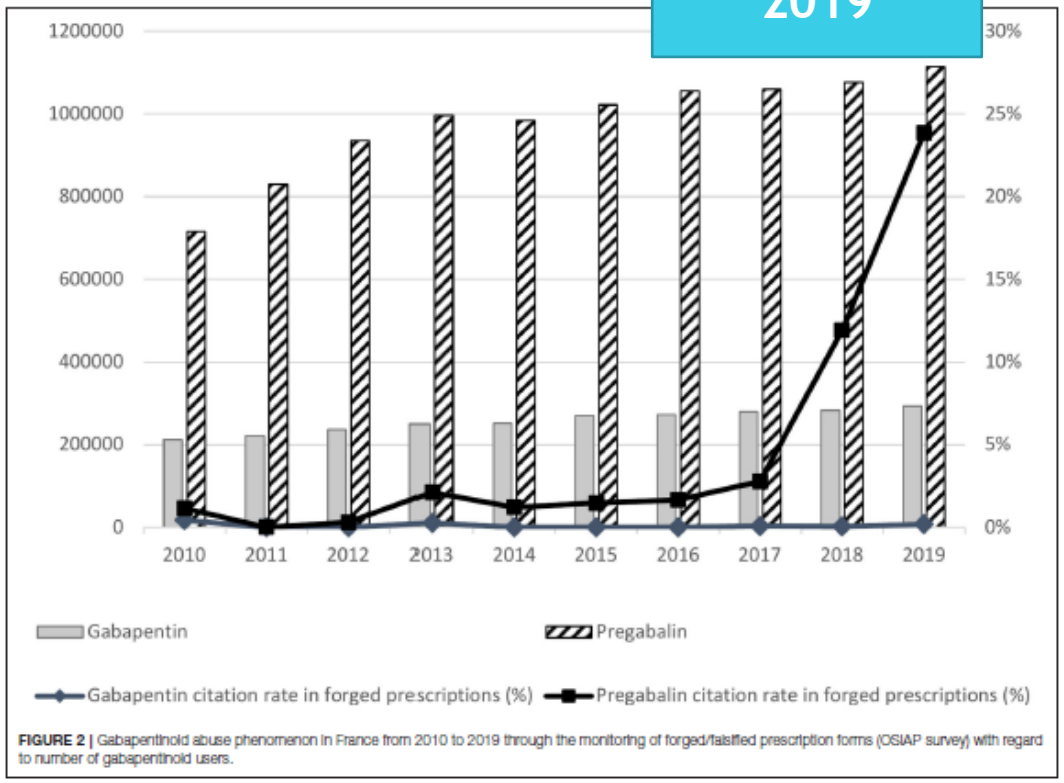


FIGURE 2 | Gabapentinoid abuse phenomenon in France from 2010 to 2019 through the monitoring of forged/falsified prescription forms (OSIAP survey) with regard to number of gabapentinoid users.

No signal for gabapentin

Tambon et al, Frontiers in Psychiatry 2021

Post marketing surveillance of abuse : Addictovigilance

Available online at www.sciencedirect.com
ScienceDirect
International Journal of Drug Policy 20 (2009) 161–169
DRUG POLICY
www.elsevier.com/locate/drugpo

Research paper

Earlier warning: A multi-indicator approach to monitoring trends in the illicit use of medicines

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Monitoring of benzodiazepine diversion using a multi-indicator approach

Vanessa Pauly[a], Elisabeth Frauger[b], Vincent Pradel[b], Sandra Nordmann[b], Laure Pourcel[c], Francois Natali[d], Vincent Sciortino[d], Maryse Lapeyre-Mestre[c], Joelle Micallef[b] and Xavier Thirion[a]

Fourteen benzodiazepine (BZD) or BZD-like medications were analyzed with three data sources aiming to assess prescription drug abuse for the year 2008. After a descriptive analysis, a principal component analysis was carried out to explore correlations between seven indicators obtained by different methods using these three different data sources and to compute a composite score of diversion for these drugs. For all the indicators, flunitrazepam appears first with much higher values than the other drugs, whereas clonazepam appears in the second or third place. These methods produce globally correlated indicators and the composite score obtained from principal component analysis ranks the drugs with the highest diversion as follows: flunitrazepam, clonazepam, oxazepam, diazepam, and bromazepam. This study shows that these methods yield consistent results. Their integration into a single multi-indicator approach gives health authorities a global view of different behaviors regarding diversion of a given drug. *Int Clin*

Psychopharmacol 26:268–277 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.
International Clinical Psychopharmacology 2011, 26:268–277
Keywords: benzodiazepines, drug reimbursement database, postmarketing surveillance, prescription drug abuse, substance-related disorder

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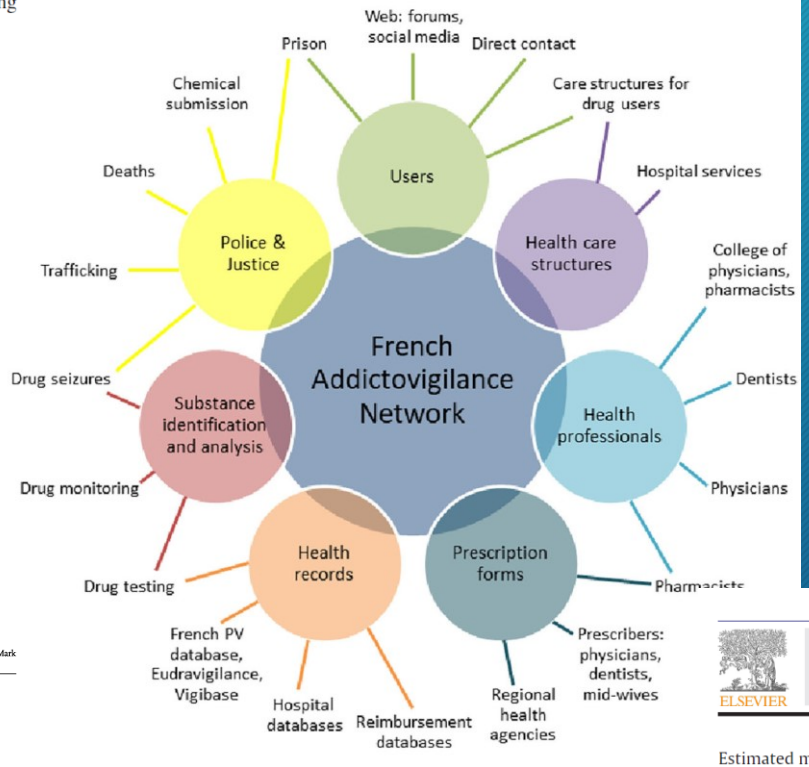


Therapie (2016) 71, 575–578
Available online at ScienceDirect www.sciencedirect.com
Elsevier Masson France EM|consulte www.em-consulte.com
ELSEVIER
Thérapie

ADDICTOVIGILANCE

Pregabalin use disorder and secondary nicotine dependence in a woman with no substance abuse history

Addiction à la prégabaline et dépendance nicotinique secondaire chez une jeune femme sans antécédent d'abus de substance

Damien Driot[a,*], Bruno Chicoulaa[a], Emilie Jouanjus[b], Julie Dupouy[a], Stéphane Oustric[a], Maryse Lapeyre-Mestre[b]

Increasing use : what about abuse at the population level?

Clin Drug Investig (2016) 36:735–742
DOI 10.1007/s40261-016-0421-z
CrossMark
ORIGINAL RESEARCH ARTICLE

Disproportionality Analysis for the Assessment of Abuse and Dependence Potential of Pregabalin in the French Pharmacovigilance Database

Jean-Baptiste Bossard[1] · Camille Pontié[2] · Julie Dupouy[1,3] · Maryse Lapeyre-Mestre[1,2] · Emilie Jouanjus[1,2]

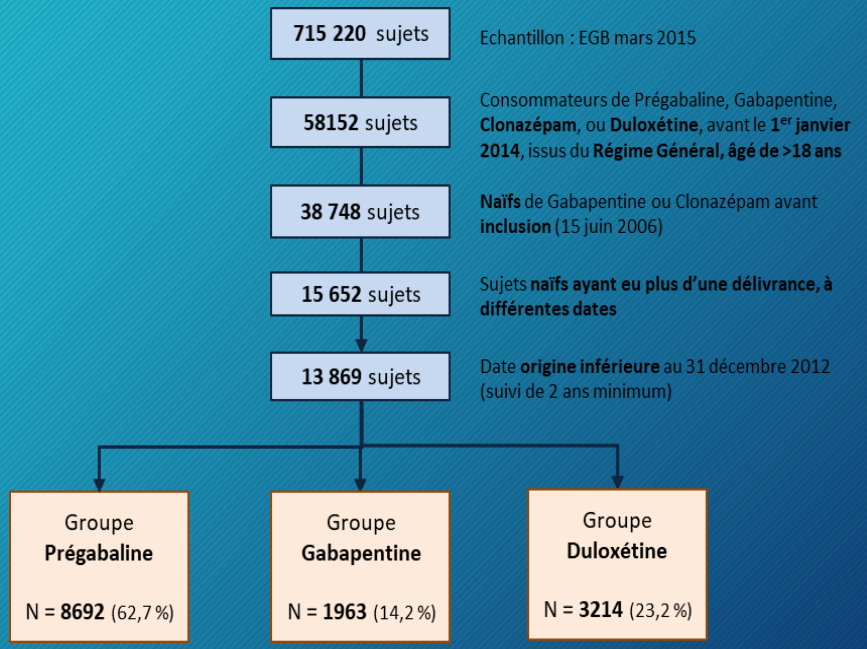
Drug and Alcohol Dependence 126 (2012) 13–20
Contents lists available at SciVerse ScienceDirect
Drug and Alcohol Dependence
journal homepage: www.elsevier.com/locate/drugalcdep
ELSEVIER

Estimated magnitude of diversion and abuse of opioids relative to benzodiazepines in France

V. Pauly[a], V. Pradel[a,b], L. Pourcel[c], S. Nordmann[b], E. Frauger[b], M. Lapeyre-Mestre[c], J. Micallef[b], X. Thirion[a,*]

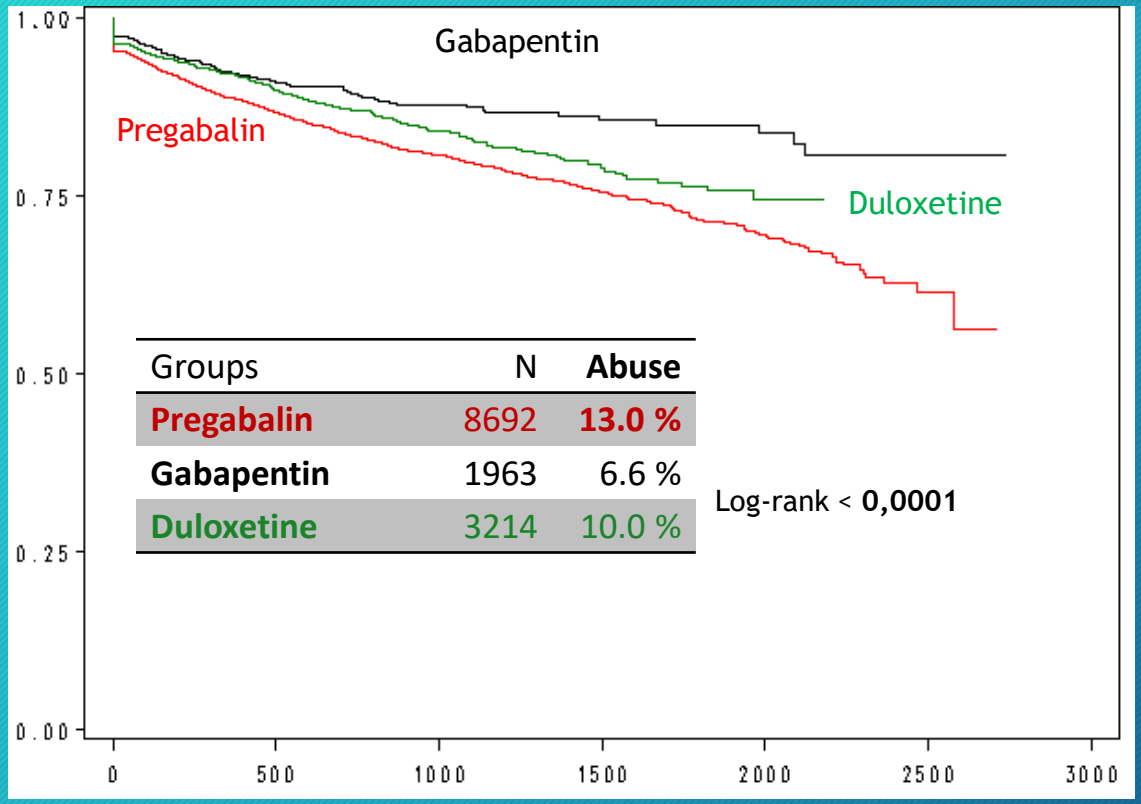
Cohort study of new users (prescription database)

- Cohort study of new users of pregabalin
  - Identified from the "Echantillon Généraliste des Bénéficiaires", EGB (1/97th representative sample of the whole French population)
  - Followed up until December 2014
- Definition of overuse :
  - daily dose > 600 mg/d (>2 DDD)
- Compared to 2 other cohorts of new users of
  - Gabapentin (gabapentinoid with same indications except anxiety) and
  - Duloxetine (antidepressant approved for neuropathic pain in diabetic patients)



Driot et al, British Journal of Clinical Pharmacology 2019

Gabapentinoid overuse



Groups	N	**Abuse**
Pregabalin	8692	**13.0 %**
Gabapentin	1963	6.6 %
Duloxetine	3214	10.0 %

Log-rank < **0,0001**

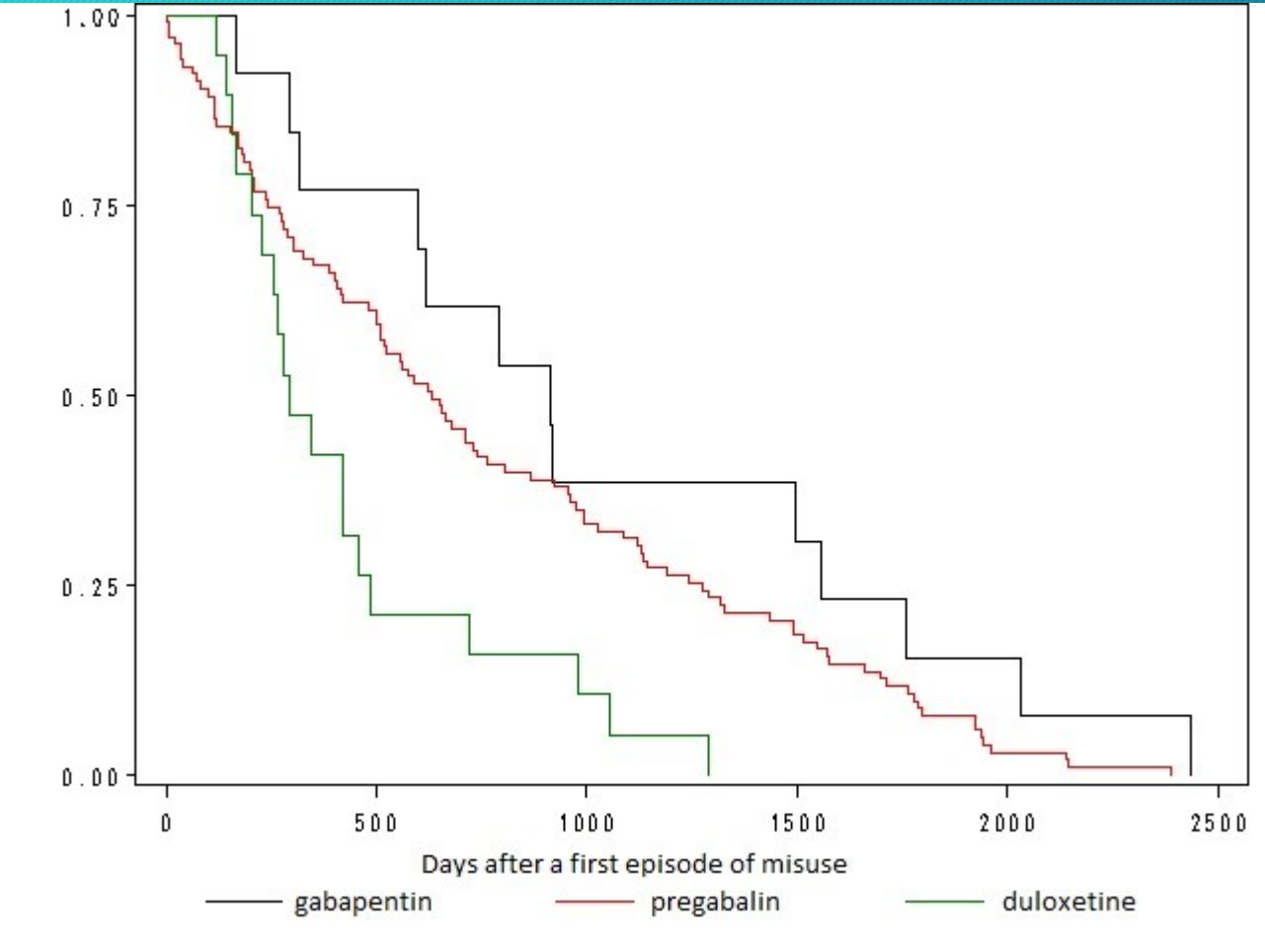
Factors associated with overuse

- Initial exposure to pregabalin
- Age 18-45 years
- Doctor shopping
- Chronic pain
- Methadone exposure (only used for opioid maintenance in France)

- Association +++ with methadone in the pregabalin cohort

Similar results for pregabalin in Sweden (8% overuse, Boden 2014) and in Denmark (10%, Schjerning 2016)

Occurrence of a primary addiction after the 1st episode of misuse



Addiction occurrence after a first episode of misuse (cumulative incidence of addiction), in the 1331 subjects with no previous history of substance disorders, according to the first used drug (pregabalin (n=960), gabapentin (n=112) or duloxetine (n=259))

The likelihood of developing a primary addiction to any substance after a first episode of misuse was 11.6% for gabapentin, 10.7% for pregabalin and 7.3% for duloxetine (log rank test: $P = 0.0019$)

Could this have been anticipated?

Meta-analysis of pregabalin safety (Zaccara 2011) : 38 RCT

- Safety profile with significant euphoria
- 1 to 12% of patients (therapeutic dose range)

Psychother Psychosom 2011;80:118–122
DOI: 10.1159/000321079

Is There a Recreational Misuse Potential for Pregabalin? Analysis of Anecdotal Online Reports in Comparison with Related Gabapentin and Clonazepam Data

Fabrizio Schifano[a, a1], Stefano D'Offizi[a, c], Michele Piccione[c], Ornella Corazza[a, b], Paolo Deluca[b], Zoe Davey[b], Giuditta Di Melchiorre[a], Lucia Di Furia[d], Magí Farré[e], Liv Flesland[f], Miia Mannonen[g], Aino Majava[g], Stefania Pagani[d], Teuvo Peltoniemi[g], Holger Siemann[h], Arvid Skutle[f], Marta Torrens[e], Cinzia Pezzolesi[a], Peer van der Kreeft[i], Norbert Scherbaum[h]

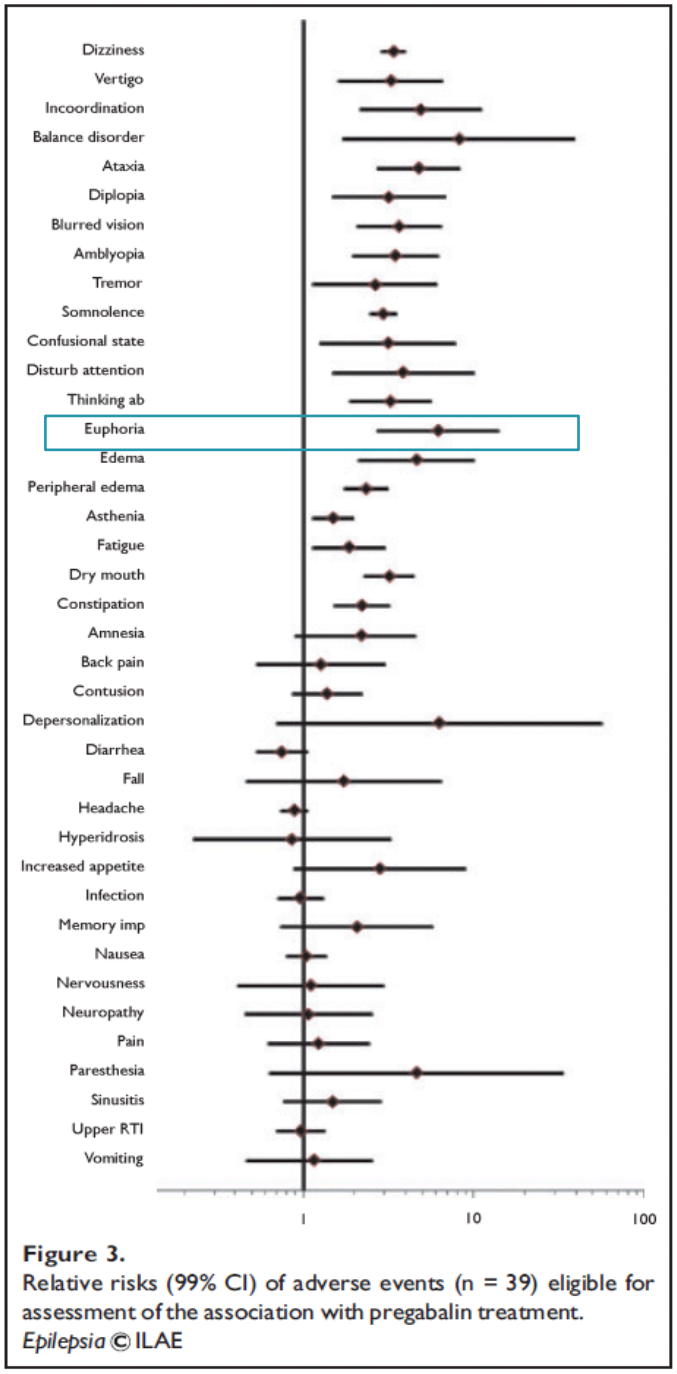


Figure 3.
Relative risks (99% CI) of adverse events (n = 39) eligible for assessment of the association with pregabalin treatment.
Epilepsia © ILAE

What should we learn from the insights of Malcolm Lader?

Addiction

MONOGRAPH

doi:10.1111/j.1360-0443.2011.03563.x

Benzodiazepines revisited—will we ever learn?

Malcolm Lader

Addiction Research Centre, Institute of Psychiatry, King's College London, London, UK

Striking similarities between BZD and gabapentinoids

abuse. Results Almost from their introduction the BZDs have been controversial, with polarized opinions, advocates pointing out their efficacy, tolerability and patient acceptability, opponents deprecating their adverse effects, dependence and abuse liability. More recently, the advent of alternative and usually safer medications has opened up the debate. The review noted a series of adverse effects that continued to cause concern, such as cognitive and psychomotor impairment. In addition, dependence and abuse remain as serious problems. Despite warnings and guidelines, usage of these drugs remains at a high level. The limitations in their use both as choice of therapy and with respect to conservative dosage and duration of use are highlighted. The distinction between low-dose 'iatrogenic' dependence and high-dose abuse/misuse is emphasized. Conclusions The practical problems with the benzodiazepines have persisted for 50 years, but have been ignored by many practitioners and almost all official bodies. The risk–benefit ratio of the benzodiazepines remains positive in most patients in the short term (2–4 weeks) but is unestablished beyond that time, due mainly to the difficulty in preventing short-term use from extending indefinitely with the risk of dependence. Other research issues include the possibility of long-term brain changes and evaluating the role of the benzodiazepine antagonist, flumazenil, in aiding withdrawal.

Conclusion

- Much evidence of abuse potential of gabapentinoids (pregabalin>gabapentin)
- Low abuse potential

BUT

- Similar to that observed with benzodiazepines

- Place in the therapeutic framework?
  - 'Banalisation'? Off-label use
  - 2nd line drugs
- Interaction with opioids
  - Respiratory depression+++
  - Without opioid overdose
- Health professionals sensitization
  - Only if needed
  - Short term use
  - Prescription reassessment

Thank you for your attention