Like Zolpidem, all sleeping pills and anti-anxiety drugs, available in pharmacies, are ineffective and dangerous « narcotics ».

Until the sleep-wake system was discovered, the cause of the paradoxical adverse effects of benzodiazepines and related drugs was unknown. The listing in the official journal of 10 January 2017 of Zolpidem (Stilnox and its generic equivalents) as a narcotic drug is an opportunity to explain why all these sleeping pills and anti-anxiety drugs are narcotics. They have unacceptable adverse effects, known as "paradoxical", as they actually exacerbate the effects they are supposed to treat.

As we will explain, benzodiazepines and related drugs are in fact psychostimulants, which is why they are considered narcotics.

Before you read this letter dedicated to the problems posed by the use of benzodiazepines and related drugs in the treatment of sleep disorders and anxiety, we recommend that you watch the following video: "Sleep disorders and how to treat them", Pr J.B. Fourtillan and Pr H. Joyeux (YouTube: duration 16 min 25).

Pr Henri Joyeux
Question 1: An order published in the official journal of 10 January 2017 has finally announced that Zolpidem (Stilnox and its generic equivalents), i.e. the medicine used as a sleeping aid, the most prescribed hypnotic in France, will now be subject to the same legislations as narcotics, due to the risk of drug dependence, abuse and misuse. What are the consequences for the patients for whom they are prescribed?

Pr Jean-Bernard Fourtillan
Starting on 10 April 2017, Stilnox and its generic equivalents will be subject to the prescription and dispensing rules which apply to narcotics. They will only be dispensed subject to a secure prescription form, i.e. featuring an anti-photocopy watermark, the number of unit doses of the drug and the duration for which they should be taken, written “in full”. To obtain another, the period indicated on the previous prescription must have completely expired.

Prescriptions of this drug should therefore decrease dramatically, which is excellent news for patients, as this drug, as with all other sleeping pills and anti-anxiety drugs, benzodiazepines and related drugs, is an ineffective and dangerous medication. Let me explain why.

Question 2: Jean-Bernard, could you tell us about the origin and meaning of the term “narcotic”?  
Originally, narcotics referred to a group of substances (essentially opiates) known to inhibit nerve centres and induce sedation-pain reduction, with “torporific” pharmacological effects.

Since the 1980s, narcotics have referred to illegal or regulated psychotropic substances; which is now the case for Zolpidem (Stilnox and its generic equivalents).
Psychotropic substances are psychoactive substances which act upon the central nervous system, and therefore on the psyche. Psychotropic substances are categorised in terms of their activity on the central nervous system (CNS).

Numerous classifications, based on the effects of these products on the CNS, have been suggested. Mention should be made of the classification developed by Jean Delay (a major French psychiatrist) along with his assistant Pierre Deniker, in 1957, as well as that of Yves Pelicier (a French physicist) and Jean Thuillier (a French psychiatrist and pharmacologist) who, in 1991, updated and modernised the Delay and Deniker classification.

However, no single classification is satisfactory, for two main reasons:

First because the action mechanisms of these drugs were unknown until our recent discovery of the Sleep-Wake system.

Antidepressants were categorised as mood stimulants (referred to as thymoanaleptics), although they act by increasing sleep by reducing vigilance, and are in fact psychosedative compounds.

Conversely, benzodiazepines and related drugs (such as Stilnox and its generic equivalents) are considered psychosedative drugs, although their paradoxical effects such as insomnia and anxiety come from their psychostimulant effects.

These effects – which you pharmacologists will understand - result from increased vigilance through the antagonism of serotonin 5-HT\textsubscript{2C} receptors (see Letter from Pr Joyeux no. 150 and "Sleep disorders and how to treat them" video);

Second, because their effects on the psyche may be reversed depending on the doses administered.

In the interest of simplification, psychotropic substances can therefore be divided into 2 categories, corresponding with opposite effects on the functioning of the central nervous system:

- Psycholeptics, or psychic sedatives, which slow down the activity of the central nervous system, such as neuroleptics (drugs used to treat psychosis);
- Psychostimulants or psychic stimulants, which increase the activity of the central nervous system (LSD, amphetamines, morphine, heroin, cocaine, ecstasy, psilocybin, mescaline, etc., which are actual narcotics).

The effects of benzodiazepines and related drugs, such as Zolpidem (Stilnox and its generic equivalents) result from two different actions well understood by the specialists:

- A stimulation of the GABA\textsubscript{A}-ergic receptors which reduces vigilance like an anaesthetic, and gives the insomniacs the impression of sleep. This sleep, known as “anaesthetic", is not restorative for the body. These drugs prevent physiological sleep, with a reduction in deep restorative sleep and a collapse of REM sleep, leading to amnesia-inducing effects (loss of memory of recent events). See: Letter from Pr Joyeux no. 150 and "Sleep disorders and how to treat them" video);

- An antagonistic action of serotonin 5-HT\textsubscript{2C} receptors, recently discovered with the Sleep-Wake system, which increases vigilance, due to the presence in the chemical structure of benzodiazepines and related drugs of the pharmacophore model of 6-methoxyharmalane, the wake hormone, a psychostimulant compound as powerful as LSD (see, on the Josefa Fund website, pages 186 to 189 of Pesp 29 of the Book: “The pineal gland and the Sleep-Wake system. Therapeutic applications”).

During the night, this “anti-sleep” action counteracts the physiological sleep induced by Valentotonin. It effectively explains the origin of the so-called “paradoxical” adverse effects of these sleeping pills and anti-
anxiety drugs (significant insomnia and anxiety), which means that benzodiazepines and related drugs are considered psychostimulants rather than psychosedative drugs.

Question 4: Jean-Bernard, could you explain why psychotropic drugs are referred to as narcotics?

A psychotropic drug’s tendency to lead to addiction is the main criterion for categorising it as a narcotic.

Addiction is characterised by two types of dependence:
- physical dependence, where the patient requires increased doses, throughout the treatment, to maintain a stable physical condition;
- psychological dependence which corresponds with the need, during the treatment, to progressively increase doses to maintain a stable psychological condition.

Question 5: Can all psychotropic drugs lead to addiction and become narcotics?

No!
Only psychotropic substances with a psychostimulating activity can lead to addiction and act as narcotics, when administered over a prolonged period.

The discovery of the wake hormone, 6-methoxyharmalan (6-MH), which increases vigilance when our body is in wake mode, via the antagonism of serotonin 5-HT\(_{2C}\) receptors, explains the development of addiction observed in all psychostimulant drugs; such as not only benzodiazepines and related drugs (Stilnox and its generic equivalents), as we have just seen, but also LSD, amphetamines, morphine, heroin, cocaine, ecstasy, psilocybin, mescaline, etc.

The chemical structures of all these narcotics share the pharmacophore model of 6-MH (see, on the Josefa Fund website, pages 186 to 189, and page 211 of the Book, and plate 43 of the Brochure, entitled: “The pineal gland and the Sleep-Wake system. Therapeutic applications”), which explains their antagonism of serotonin 5-HT\(_{2C}\) receptors and the psychostimulating effect, via the resulting increase in vigilance.

Question 6: How do you explain the development of addiction to Stilnox® and all benzodiazepines and related drugs, which leads to these drugs being referred to as “narcotics”?

To give a rough outline of the addiction phenomenon of all psychostimulating psychotropic substances, particularly benzodiazepines and related drugs, one only has to examine their actions on the body during the nightly rest period.

When the body is in sleep mode, these drugs counteract, like 6-methoxyharmalan, the remedial actions of Valentonin on the body’s psychic and vegetative lives. So much so that, during the day, when the treatment is prolonged, the body is increasingly tired. In order to cope and maintain a stable physical and psychological condition, the subjects are forced to indefinitely increase the doses.

Therefore, as I have just pointed out, all benzodiazepines (Lexomil, Temesta, and their generic equivalents, etc.) and related drugs (Stilnox, Imovane, and their generic equivalents) are psychostimulating drugs which can lead to addiction, with a physical and psychological dependence, when used over a prolonged period of several months.

This toxicity, common to all these sleeping pills and anti-anxiety drugs, is well known and has been described in the Vidal dictionary for decades.
It is a wonder why it has taken so long to categorise Zolpidem as a narcotic, and why all other benzodiazepines and related drugs, which have exactly the same drawbacks, were not included in the list of Narcotics at the same time as Zolpidem.

Ultimately, thanks to the discovery of the Sleep-Wake system, we have demonstrated and can affirm that any compound with a psychostimulating activity is a narcotic.

Question 7: We have just seen why all sleeping pills and anti-anxiety drugs currently available in pharmacies are narcotics, when administered over a prolonged period. These are therefore dangerous products. Are they sufficiently effective to justify, despite their toxicity, their prescription for insomniac and anxious subjects?

No!

These drugs, whose toxicity we have just reiterated, are not only ineffective in the treatment of sleep disorders and anxiety, they also destroy physiological sleep due to their anti-sleep effect. Their adverse effects, referred to as “paradoxical”, linked to their narcotic characteristics, therefore exacerbate the effects for which they are prescribed.

In France, the 3 most commonly used sleeping pills are Stilnox, Lexomil, Temesta and their generic equivalents. These drugs belong to the benzodiazepine family (Lexomil, Temesta and their generic equivalents) and related drugs (Stilnox, Imovane and their generic equivalents). Contrary to the claims featured in their monographs in the Vidal dictionary, these drugs are neither hypnotics nor anxiolytics.

In the Vidal dictionary, the indications of Lexomil and Temesta recommend using them in the “symptomatic treatments of severe and/or debilitating anxiety”. For Stilnox, indications are limited to the “treatment of occasional” (“such as, for example, during a trip”) and “transient insomnia” (“such as the occurrence of a serious event”), with the shortest possible treatment durations: “2 to 5 days for occasional insomnia”, and “2 to 3 weeks in case of transient insomnia”.

In this regard, on reading the monograph of Stilnox in the Vidal dictionary, it is surprising that the treatment of sleep disorders in subjects suffering from insomnia, large in number and the highest consumers of this drug, does not feature among the indications of this so-called sleeping pill.

The monographs of these 3 drugs are identical and common to all benzodiazepines and related drugs. The dosage/administration, contraindications, warnings, precautions, interactions, adverse reactions, overdosage, pharmacodynamics sections are almost identical word for word.

The pharmacodynamics section, which is supposed to justify their indications, specifies the pharmacodynamic properties common to all compounds in the benzodiazepines and related drugs class. All specialists will easily understand these properties:

- **myorelaxant**: which causes muscular weakness, responsible for hip fractures in the elderly;

- **anxiolytic**: which is untrue, as indicated by the adverse effects, paradoxical for an anxiolytic, such as significant anxiety, restlessness, nervousness, etc. These drugs create anxiety and maintain depression;

- **sedative**: which is untrue, as indicated by the paradoxical adverse effects such as restlessness, nervousness, delusions, hallucinations, etc.;

- **hypnotic**: which is untrue as, on the one hand, these drugs provide the body with non-restorative anaesthetic sleep and, on the other hand, one of their frequently observed adverse effects is insomnia, which is somewhat ironic for a so-called sleeping drug;

- **anticonvulsant**: linked to their GABA-ergic activity;
- **amnesia inducing**: correlated with the suppression of REM sleep. They are initially responsible for the loss of memory of recent events (anterograde amnesia), and subsequently for memory loss in the elderly.

They aggravate the clinical symptoms of insomniac and anxious patients. They believe they are taking a sleeping pill when in fact their sleep disorders are exacerbated and they suffer from unacceptable adverse effects, due to their psychostimulating properties. Because they were hitherto unexplained and exacerbate the effects for which they are prescribed, they have been referred to as “paradoxical” adverse effects.

**Question 8:** For all treatments of neurological disorders caused by a shortage of pineal hormone secretions, such as sleep disorders, nervous breakdowns or Parkinson’s and Alzheimer’s neurodegenerative diseases, we have seen that the only possibility is to use transdermal patches containing VLT and 6-MH, applied during the night.

**What if we want to stimulate the body during the day?**

6-MH and VLT are the day and night hormones which control, thanks to their opposite actions during the rest and activity phases, how numerous organs involved in our psychic (thoughts and dreams) and vegetative lives (respiratory, cardiac, intestinal functioning, etc.) function.

For the sleep-wake regulation, Valentonin, the sleep and night hormone, must be administered at the same time as 6-methoxyharmalan, the wake and day hormone, to avoid destabilising the Sleep-Wake system (see Letter from Pr Joyeux no. 147). To achieve harmonious regulation of the body during the 24 hours of the nyctohemeral cycle, it is imperative to ensure that the sleep hormone prevails during the night and the wake hormone prevails during the day.

Thus, should the hormonal secretions of the pineal gland be deficient (sleep disorders, nervous breakdowns, neurodegenerative diseases such as Parkinson’s and Alzheimer’s, etc.), a substitution treatment must be implemented to offset this insufficiency, by simultaneously administering the 2 hormones and identically reproducing the conditions of their physiological secretions.

They must therefore be administered during the secretion period of the pineal gland, i.e. for approximately 8 hours; and they must be released in the bloodstream at a constant rate.

**One of the major consequences of the discovery of the Sleep-Wake system lies in the conditions of use of psychotropic substances.**

As they act for 24 hours, they all disrupt the functioning of the body when it is in sleep mode or wake mode:
- the administration of a psychostimulating drug counteracts the remedial actions of Valentonin (VLT) during the night, which exposes patients to numerous adverse effects such as insomnia and anxiety, which makes them indefinitely increase the doses in order to maintain a stable physical and psychological condition, due to an addiction phenomenon;
- conversely, the administration of a psychosedative drug reduces the stimulating action of the wake hormone, 6-MH, during the day.

This brings us to the conclusion that the only way to influence the activity of the central nervous system, to stimulate it during the day or reduce it during the night, without disrupting the balance of the Sleep-Wake system, i.e. without adverse effects, is the transdermal administration of the combination of the 2 wake and sleep hormones. This is achieved by using transdermal patches, applied in the evening at bedtime and removed when waking up in the morning, capable of releasing VLT doses 4 times higher than those of 6-MH in the body.
It is a genuine revolution in the design and administration of psychiatric treatments, which signals the end of current psychotropic drugs.

Pr Henri Joyeux and Pr Jean-Bernard Fourtillan

Post-scriptum

On the Fonds-Josefa.org website to whom Pr Jean-Bernard Fourtillan and his wife have assigned all registered patents:

– Book and Brochure "The pineal gland and the Sleep-Wake system. Therapeutic applications"

– YouTube videos:

"The pineal gland and the Sleep-Wake system. Therapeutic applications", Pr J.B. Fourtillan (YouTube: duration 37 minutes)

"Pr JB Fourtillan answers Pr H Joyeux's questions", Pr J.B. Fourtillan and Pr H. Joyeux (YouTube: duration 1 hour)

"The Sleep-Wake system in Creation", Pr J.B. Fourtillan (YouTube, duration: 14min 35s + 2min 13s)

"The causes and treatment of Alzheimer's disease finally discovered" Pr J.B. Fourtillan and Pr H. Joyeux (YouTube: duration 13min 30s)

"The real causes and treatment of Parkinson's disease", Pr J.B. Fourtillan and Pr H. Joyeux (YouTube: duration 14min 25s)

"Sleep disorders and how to treat them", Pr J.B. Fourtillan and Pr H. Joyeux (YouTube: duration 16 min 25)

"The causes and treatment of nervous breakdowns", Pr J.B. Fourtillan and Pr H. Joyeux (YouTube: duration 13min 15s)

– Donations can be made to help the Josefa Fund finance, independently of the pharmaceutical industry, the development and manufacturing of patches until the TUA (Temporary Use Authorisation) is granted, which is scheduled for the summer of 2017.