Explained depression will be treated better, thanks to transdermal administration of the 2 pineal sleep and wake hormones

Dear Friends,

What news in a short amount of time, these recent months!
I imagine how astonished you must be by so many claims, following the very important discovery by my colleague and friend Pr Jean-Bernard Fourtillan. Fortunately, it is well protected from risks of financial abuse which exploit patients more than they protect them.
We are embarking on a new therapeutic course. In addition to the many patients who are impatiently awaiting the patches we have promised, many physicians have already written to me with their questions. There are the incredulous, the passionate who have well understood the prospects, and those who criticise without seeking to understand, using outmoded arguments, for example that I have been struck off the council of the order of physicians, which is inaccurate, and that "*Pr J.B. Fourtillan and Pr H. Joyeux are retired and should play golf*". They know nothing about us.

We already clearly understand the obstacles that await us. We do not fear them, because they are in service of the general public.

To return to the subject of this 150th letter, it should be recalled that French specialists and general practitioners are the world champions of prescribing antidepressants. Beyond this excessive prescribing, undoubtedly encouraged by pharmaceutical Laboratories, they should know that, **on the pretext of helping patients sleep better, soporific and anxiolytic medicines, i.e. benzodiazepines and related drugs (such as Stilnox®), should never be prescribed to a patient taking antidepressants.**

Antidepressants and sleeping pills are incompatible. This is made clear in this new letter. No one will be surprised by this, since the health authorities have just classified Zolpidem (Stilnox® and its generics), without also knowing why, in the category of narcotics. However, all narcotics are psychostimulant medicines that, by increasing vigilance and anxiety, maintain and promote nervous breakdowns.

Before reading the following letter, in which I interview Jean-Bernard Fourtillan, I advise you to watch attentively the video: **"The causes and treatment of nervous breakdowns"**, Pr J.B. Fourtillan and Pr H. Joyeux (YouTube: duration 13min 15s).

Pr Henri Joyeux

Question 1: Jean-Bernard, the discovery of the sleep and wake hormones enables us to understand the mechanism of nervous breakdowns. Why can nervous breakdowns be compared to transient sleep disorders?

J-B Fourtillan - In depressed subjects the level of vigilance is increased by the stress triggered by the occurrence of one or more unfortunate events. When the quantity of Valentonin, the sleep hormone, secreted during the night, is insufficient to lower and maintain vigilance below the sleep barrier, we no longer sleep.

A series of sleepless nights exhausts the body and leads to depression. That is why insomnia and anxiety are the two characteristic symptoms of nervous breakdown.

The efficacy of antidepressants, of which the discovery of the Sleep-Wake system enabled me to specify the modes of action, confirms this triggering mechanism of nervous breakdown. Antidepressants act by increasing sleep, by decreasing vigilance.
When the cause of the stress, at the origin of the depression, has disappeared, the subjects sleep as usual; this is the end of the depression. Sleep becomes truly restorative.

Question 2: By what mechanisms do antidepressants act?

The mechanism of nervous breakdown and the mode of action of antidepressants are now explained by the respective roles of two neurotransmitters, Noradrenalin and Serotonin.
Discovery of the Sleep-Wake system enabled us to elucidate the mode of action of the two types of antidepressants,

- one, **Noradrenalin Reuptake Inhibitors (NRI**), such as Clomipramine (Anafranil® and its generics), indicated in "*major depressive episodes, obsessive-compulsive disorders and the prevention of panic attacks with or without agoraphobia"* but responsible for very frequent drowsiness.
- the other**,** competitors of the preceding on the antidepressant market**, Serotonin Reuptake Inhibitors (SRI)**, such as Fluoxetine (Prozac® and its generics), do no better in the same indications.

In depressed subjects, the Sleep-Wake system is quantitatively normal, as attested by the similarity of the pineal productions of Melatonin, a sleep marker (see Letter 147), in normal subjects and in depressed subjects not treated by antidepressants (E. PALAZIDOU, 2).
But, to help depressed subjects sleep, the Sleep-Wake system must be strengthened, taking into account the stress-related increase in vigilance.

Question 3: How did you demonstrate the mode of action of Noradrenalin Reuptake Inhibitor (NRI) antidepressants like Anafranil® and its generics? And of Serotonin Reuptake Inhibitor (SRI) antidepressants?

Following the work of E. PALAZIDOU (1, 2), an increase in Melatonin secretion by the pineal gland was observed (demonstrated by measuring its plasma concentration). It followed stimulation of the noradrenergic receptors located on the pinealocytes (pineal gland cells), and is commonly used, by pharmaceutical Laboratory pharmacologists, to measure the strength of Noradrenalin reuptake inhibition by NRI antidepressants like Clomipramine (Anafranil®).

The increase in Melatonin secretion by the pineal gland is thus an indicator of the strength of action of an NRI-type antidepressant.

Of course, the researchers were unaware, before my discovery, that this noradrenergic stimulation of the pinealocytes constitutes, on its own, the mode of action of NRI antidepressants.
Indeed, by increasing Noradrenalin concentrations at the noradrenergic receptors of the pineal gland, by inhibition of its reuptake by the presynaptic neurons, NRI antidepressants stimulate all day long, for 24 hours, the simultaneous synthesis of the 3 pineal hormones, not only Melatonin (MLT), but also 6-Methoxyharmalan (6-MH) and Valentonin (VLT).

This surplus of VLT enables, by activation of 5-HT_{2C} serotoninergic receptors, a decrease in vigilance and a restoration of sleep. In addition, this work shows, contrary to the theories usually put forth, that the pineal secretion of MLT is not reduced in depressed subjects not treated with antidepressants, compared to normal controls.

The discovery of the Sleep-Wake system thus makes it possible to understand how increases in Noradrenalin and/or Serotonin concentrations, throughout the CNS, consecutive to inhibitions of their reuptake, lead to an increase in serotoninergic transmission at the 5-HT_{2C} receptors, caused by Serotonin and/or Valentonin.

In depressed subjects, whose vigilance level is too high to be able sleep under conditions of normal pineal production of VLT, serotoninergic transmission at the 5-HT_{2C} serotoninergic receptors can be amplified in two ways:

- either by increasing Serotonin concentrations at the 5-HT_{2C} receptors, with SRI antidepressants;
- or following an increase in Noradrenalin concentrations at the pinealocyte noradrenergic receptors with NRI antidepressants, by increasing the concentrations of Valentonin, which will activate the 5-HT_{2C} receptors by allosteric stimulation.

In short, with the 2 types of NRI and SRI antidepressants, the reduction in vigilance that results from the stimulation of 5-HT_{2C} serotoninergic receptors makes it possible to restore sleep in depressed subjects.

Question 4: The principle of depression treatment thus consists in restoring sleep by stimulating 5-HT_{2C} serotoninergic receptors to decrease vigilance. What are the characteristics of an ideal antidepressant treatment, which would make it possible to achieve this goal, without disturbing the sleep-wake cycle, while being devoid of undesirable effects?

As I have just made clear, the most used antidepressants, NRI, SRI, or SNRI antidepressants with mixed action, act by increasing sleep by direct (SRI) or indirect (NRI) activation of 5-HT_{2C} serotoninergic receptors.

But these medicines have major disadvantages:

- first, the inhibitions of Serotonin and Noradrenalin reuptake are not selective. They occur for all serotoninergic and noradrenergic receptors of the body, which causes a great many undesirable effects;
- moreover, they act 24 hours a day, whereas the inhibition of reuptake should occur only during the night.

They thus cause a dysregulation of function of the entire body, creating a permanent hypnotic action that makes the subjects atonic, therefore inactive and often apathetic during the day;

- finally, antidepressants have no (SRI like Prozac®) or little (NRI like Anafranil®, and SNRI like Effexor®) action on secretion of 6-Methoxyharmalan, the vigilance hormone, and do not restore to the depressed subjects the physical and mental energies they lack.

These three major disadvantages considerably limit the efficacy of these medicines.

Question 5: Explain to us why the dual-compartment transdermal patches, which separately contain the 2 natural sleep and wake hormones, will constitute the ideal treatment for nervous breakdown?

To help depressive people sleep, without disturbing the normal course of the sleep-wake cycle, it is necessary to introduce the 2 hormones into the bloodstream in the manner of the pineal gland. To thus stay closest to what our normally functioning body is accustomed.
Thus, as for treating insomnia, Valentonin and 6-Methoxyharmalan will be administered, in combination, during the night at the times they are manufactured by the pineal gland.
The administration modalities are extremely crucial. They must make it possible to reproduce, as exactly as possible, the curves of physiological secretion of the two hormones.
In practice, only transdermal administration, in the form of dual-compartment patches containing Valentonin and 6-Methoxyharmalan in a 4 to 1 ratio, makes it possible to meet these conditions.
The patch must be applied in the evening at bedtime and removed when waking in the morning. This is to respect the schedules of the sleep and waking modes.
It is thus a treatment with two natural hormones, Valentonin and 6-Methoxyharmalan.
It is administered during the secretion period, and reproduces pineal secretion, while increasing it.
The doses resorbed, i.e. delivered to the body, during 8 hours, correspond to the physiological secretions: 50 microgrammes of 6-Methoxyharmalan and 200 microgrammes of Valentonin. These doses will be those of the patches used to treat sleep disorders and nervous breakdowns.
This treatment will guarantee the absence of undesirable effects.

Question 6: Why treat depressed subjects with the same treatment as for insomniacs?

As I said before, nervous breakdowns are transient sleep disorders. It is thus necessary to treat them like sleep disorders, but only during the period of depression. The time that everything returns to order.

Question 7: Is it wise to administer psychostimulant medicines to depressed subjects, on the pretext of increasing their energy, and thus to improve the treatment of depression?

In the mind of the general public, depression is perceived as a pathologic state characterised by a lack of energy and dynamism of mental activity. That is true, but it is only the consequence of the lack of sleep that leads to the depressive condition. The series of sleepless nights ends up exhausting the depressed subjects.

In depressed subjects, the Sleep-Wake system must be strengthened, because if secretion of the sleep hormone, VLT, is insufficient, the same will obligatorily be true for that of the wake hormone, 6-MH, which conditions the state of vigilance during the day.
These 2 hormones do not go one without the other, to ensure harmonious regulation of mental life.

It is, I repeat, one of the shortcomings of antidepressants that act primarily on sleep, and more particularly for SRI (Serotonin Reuptake Inhibitor) antidepressants, such as Prozac®, Deroxat®, Seropram®,

Seroplex®, or Zoloft® and their generics. These antidepressants act only by increasing sleep, not only during the night, but 24 hours a day. During the day, the reduction in vigilance, due to the action of these antidepressants, decreases the mental and physical energies of the treated subjects.

To combat this state of fatigue, observed in depressed subjects treated with these antidepressants, researchers, who still do not know the mechanism of depression, naturally imagined to administer various psychostimulant medicines such as Xeroquel®, Zyprexa®, Leponex®, Risperdal®, and even hallucinogenic psychostimulants such as Psilocybin or LSD, or cannabinoids.

However, all these compounds, and others like benzodiazepines and related drugs, are, because of their chemical structures, 5-HT_{2C} serotoninergic receptor antagonists, which certainly increase vigilance during the day, but which unfortunately oppose sleep during the night. That has the major disadvantage of aggravating insomnia and anxiety in the treated depressed subjects. The same therapeutic error is made when they are used to treat bipolar disorders. In this area, even specialists recognise that there is much therapeutic abuse.

All these medicines are incompatible in combination with antidepressants in the treatment of nervous breakdowns and bipolar disorders.
The only possible treatment is to strengthen the Sleep-Wake system by simultaneously increasing the concentrations of the 2 pineal sleep and wake hormones in the body.

Question 8: Since the 2 characteristic symptoms of depression are insomnia and anxiety, what could be the place of benzodiazepines and related drugs that are prescribed to depressed patients, due to their "alleged" soporific and anxiolytic properties?

Anxiety, the fear that an unhappy event will occur, being one of the principal symptoms of depression, the first measurement that comes to the mind of patients and their physicians is to resort to anxiolytics, i.e. benzodiazepines (Lexomil®, etc.).

Likewise, physicians tend to prescribe the same benzodiazepines and related drugs (Stilnox®, Imovane®, and their generics) to depressed subjects, on the pretext of helping them sleep better.
In both cases, it is exactly the opposite that occurs, since, like the psychostimulant products of which I just spoke, and for the same reasons we touched on in Letter number 147 and in the video: **"Sleep disorders and their treatment",** (Pr J.B. Fourtillan and Pr H. Joyeux; YouTube: duration 16min 25s), **benzodiazepines and related drugs have anti-sleep effects, and amplify depression, by these depressogenic and anxiogenic effects.**

Question 9: Do antidepressant medicines make the cause of depression disappear?

No! But they make it possible to better endure it, thanks to their action on sleep. Psychotherapy, combined with antidepressants, is without doubt very useful for accelerating recovery from nervous breakdown.
I repeat: when stress, the cause of depression, disappears, subjects sleep normally again; it is the end of the depression.

Question 10: Are we all predisposed to nervous breakdown in the same way?

Measurement of the melatonin concentration in the blood plasma, in the middle of the night (**"marker"**), shows considerable variations in secretion of the 3 pineal hormones, in human beings.
The occurrence of an unfortunate event that leads certain people to depression will not have the same depressogenic effect in other individuals. And it is likely that people whose pineal hormone secretions are high do not sink into depression as easily as others when they are confronted with the same adversities.
It is logical to think that recurrent, or endogenous, depression affects individuals who have low pineal secretions, such that they fall into a depressive state at the least adversity. By strengthening their Sleep-Wake system, the dual-compartment transdermal patches, containing VLT and 6-MH, should cure them and change their lives.

Question 11: Why do Alzheimer's and Parkinson's patients have nervous breakdowns, particularly when they learn of the disease of which they are victims?

Parkinson's and Alzheimer's diseases are neurodegenerative ailments caused by greatly reduced secretions of pineal hormones, indeed collapsed in Alzheimer's patients. All these patients have sleep disorders, connected to a substantial drop in the secretion of Valentonin, the sleep hormone. They are thus particularly vulnerable to nervous breakdown, especially at the time of the medical diagnosis. In most cases physicians prescribe antidepressants to them, which only aggravate the situation.

Question 12: Jean-Bernard, can you tell us, to answer the question most frequently asked by readers of my letter, when the transdermal patch will be available?

We are in the process of having specialists finalise the manufacture of the dual-compartment patches. The ready-to-use patches will be available at the end of the second quarter of 2017.
First, we want to retain our independence, with respect to pharmaceutical Laboratories, and control of the development process until the patches are finalised and manufactured.
Our ambition is to make the transdermal patches, containing Valentonin and 6-Methoxyharmalan, available to patients during the 3rd quarter of 2017.

This within the framework of a Temporary Use Authorisation (TUA), which can be granted, while awaiting a Marketing Authorisation (MA), in very specific cases, for discoveries that provide solutions to diseases which are considered serious and for which no suitable treatment exists.

To help the Sister Josefa Menéndez Fund to finance, independently of the pharmaceutical industry, these operations until the TUA for the patches is granted, scheduled for the summer of 2017, readers of your letter can make donations to the Sister Josefa Menéndez Fund, which are tax deductible, either by bank card (by clicking on the **Donations** link), or by cheque payable to: Sister Josefa Menéndez Fund, sent to the following address: 19, rue du Pré l'abbesse, 86000 Poitiers, France.

The numerous emails received on this topic attest to the tremendous interest generated by the dissemination of this discovery. The rising, even alarming number of people who discover the first signs of Parkinson's and/or Alzheimer's disease or claim to suffer from sleep disorders at an increasingly early stage in our disorientated society, have encouraged us to let you know about the incredibly positive consequences of this discovery.

Do not hesitate to broadly circulate the information to those around you. All retirement homes should know. Treatments are coming, so help us publicise them before we can make them widely available to the general public.

May the new year bring you and your family better health and wellbeing.

Pr Henri Joyeux

Post-Scriptum

On the **Josefa Fund website** to which Pr Jean-Bernard Fourtillan and his wife have entrusted all patents filed:
– 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 treatments of Parkinson's disease**", Pr J.B. Fourtillan and Pr H. Joyeux (YouTube: duration 14min 25s)
"**Sleep disorders and their treatment**", Pr J.B. Fourtillan and Pr H. Joyeux (YouTube: duration 16min 25s)

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.

Sources

(1) Palazidou, E., Beer, M., Checkley, S.A. & Stahl, S. Pharmacologic exploitation of neurotransmitter receptors for the design of novel antidepressant drugs. Drug Design and Delivery, 2, 247-256 (1988).
(2) Palazidou, E., Papadopoulos, A., Ratcliff, H., Dawling, S. & Checkley, S.A. Noradrenaline uptake inhibition increases melatonin secretion, a measure of noradrenergic neurotransmission, in depressed patients. Psychological Medicine, 22, 309-315 (1992)