

Anticipatory anxiety of seizures: What is the best treatment?

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ABSTRACT

Anxiety disorders affect roughly 25% of people with epilepsy (PWE), and are associated with a strong impairment of quality of life and a poorer stabilization of epilepsy. Anticipatory anxiety of seizure (AAS), defined by the persistent worry or fear to have another seizure, is highly frequent and associated with avoidant behavior. Unfortunately, AAS is often overlooked and untreated. Here, we present the case of a 35-year-old patient suffering from AAS secondary to focal epilepsy. We aimed to provide practical guidelines and tools for the screening and treatment of anxiety disorders in PWE. Regarding psychotropic medication, Sertraline or Citalopram might be good options for first-line treatment of AAS, since they are efficient against anxiety and well-tolerated in epilepsy.

Illustrative case study: A 34-year-old woman with constant worrying and severe fear of seizures

A. History of epilepsy

The patient was a 35-year-old woman diagnosed with postsurgical focal epilepsy following the operation of a right dermoid cyst in 2008, which led to the initiation of an antiseizure medication. The treatment was discontinued in 2010 by the neurosurgeon since there was no recurrence of seizures. From 2015 to 2018, epileptic seizures reappeared, and patient was treated with carbamazepine 400 mg (twice a day), Lamotrigine 100 mg (twice a day), and Bromazepam 6 mg (1/2 to 1 tablet per day, on demand, prescribed by her general practitioner). In December 2021, the patient had been seizure-free for more than 28 months, but the neurologist noted a severe worrying of having another seizure, which led Ms. V to refuse the decrease in lamotrigine. The neurologist referred her to the psychiatric consultation and Cognitive-Behavioral Therapy (CBT) (Fig. 1).

B. Psychiatric assessment

The psychiatrist assessment had to figure out whether anxiety was *peri-ictal* or *interictal*, and epilepsy-specific or not. After the onset of epilepsy, the patient has feared to have another seizure since a seizure occurred while she was preparing her baby's bath in 2015. Thus, she thought to be dangerous for her daughter because of seizures. She avoided all situations where she might be alone with her daughter. She also suffered from numerous avoidant behaviors, and an obsession of avoiding sleep deprivation with the need to take naps even when she

was not tired. Moreover, she also had symptoms of other anxiety disorders, such as weekly panic attacks, avoidance of social situations (speaking out of people, risk of having a seizure in front of people). Those anxious symptoms did not have any chronological link with the occurrence of seizure. The psychometric assessment by GAD-7 found a score of 13 (threshold is 7).

Regarding the psychiatric history before the onset of epilepsy, she always has had difficulties at school when speaking in front of others, and already had several panic attacks during adolescence with periods of agoraphobia but it resolved.

C. Psychiatric treatment.

On the pharmacological part, escitalopram (antidepressant) was started at 10 mg, increased to 15 mg and then to 20 mg over 4 months. The treatment by bromazepam was decreased to ¼ tablet in the evening only. On the psychological part, she received CBT with psychoeducation about anxiety disorders and exposure exercises.

The effectiveness was satisfactory with a quick disappearance of panic attacks, agoraphobia, and a global improvement of quality of life. She could be alone with her daughter. She was also more at ease when speaking up in front of colleagues, and less afraid of being judged by others. She stopped programming systematic naps and went out with friends during the evening.

Brief discussion of the psychiatric diagnosis

Clinical signs and symptoms

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<https://doi.org/10.1016/j.ebr.2024.100673>

Received 29 January 2024; Received in revised form 6 May 2024; Accepted 6 May 2024

Available online 8 May 2024

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Fig. 1. Pragmatic recommendations for neurologist with people with epilepsy (PWE).

The nomenclature of anxiety disorders in PWE is complex, and we discussed the diagnoses of this patient according to a previous proposition of classification[1]. First there are the named “peri-ictal anxiety symptoms” which are chronologically related to seizure (before, during and after the seizure). Since the patient did not have seizure for more than 2 years, we can exclude the diagnosis of peri-ictal anxiety disorders. Furthermore, she never reported ictal fear (or anxiety) and could not remember her attacks. Secondly there are the named “interictal anxiety disorders” with no chronological link to seizure. Regarding interictal anxiety, we need to distinguish epilepsy – specific and non-specific disorders.

Epilepsy-specific interictal anxiety disorders

- Anticipatory anxiety of seizure (AAS): is clearly present as a specific invasive symptom, with a persistent fear of having a seizure all day long. She described obsessive thoughts about this fear, which even led to attention problems. This anticipatory anxiety could be associated with various restrictive and avoidant behaviors (i.e., avoid going out, social withdrawal, or conversely avoid being alone...). There is a strong impairment of quality of life, secondary to excessive worries and/or avoidance symptoms.
- Epileptic social phobia: worrying about the presence of witness during an epileptic seizure, by describing seizures as “repulsive, disgusting, humiliating.”
- Seizure phobia: being terrified of having another seizure at a severity level stronger than AAS. The patient even refuses to use vocabulary related to epilepsy (never said “seizure,” or “epilepsy,” even to her relatives). The patient is not able to cope with watching a video of her own seizure or being witness of another patient’s seizure. She developed irrational behaviors specifically to prevent seizures: cannot take her antiseizure medication more than 5 min later than usual, having excessive naps or suppress definitively any food that she related to seizures.

Non-specific interictal anxiety disorders:

- Panic disorder: repetition of panic attacks and agoraphobia. It is not an epileptic panic disorder because (a) the patient did not confound a panic attack with an onset of epileptic seizure, (b) the onset of panic disorder was anterior to the epilepsy.
- Social anxiety: fear of speaking in public, fear of being negatively judged by others.

Differential diagnosis

Given the severity of anxiety and its consequences, the hypothesis of generalized anxiety disorder (GAD) could be evoked. GAD is defined by an excessive worry about a variety of topic (more than two), associated with physical and cognitive symptoms. Nonetheless, our patient had

Table 1

Distinction between the different diagnoses of anxiety disorders in people with epilepsy (PWE).

Peri-ictal anxiety symptoms	Interictal anxiety disorders	
Need the occurrence of epileptic seizure	No chronological link with epileptic seizure	
Pre-ictal: before the seizure	Specific of epilepsy: anxious symptoms about seizure (occurrence out of public, worrying of another seizure, confusion of panic attack with seizure...)	Nonspecific: Anxious symptoms correspond to disorders described in DSM-V
Ictal: during the seizure		
Post-ictal: after the seizure		
<i>In our patient: no peri-ictal anxiety symptoms because she had no seizures anymore</i>	<i>In our patient: Anticipatory anxiety of seizures Epileptic social phobia and seizure phobia</i>	<i>In our patient: Panic disorder, Social Anxiety</i>

excessive thoughts focused solely on epilepsy or panic attacks. The high score on the GAD-7 scale may be related to the several epilepsy-specific anxiety disorders rather than GAD itself. Moreover, the rituals for taking medication at the right time or taking naps did not resemble to compulsions, and the diagnoses of obsessive-compulsive disorder, or obsessive personality could be eliminated. There were no associated

Table 2

Items of the Epilepsy Anxiety Survey Instrument (EASI) screening for AAS and related symptoms [4].

Item 5	I found it difficult to stop worrying about having a seizure 0 = Not at all 1 = Several days 2 = More than half the days 3 = Nearly every day
Item 7.	If I feared something might trigger a seizure, I avoided it completely. 0 = Not at all 1 = Several days 2 = More than half the days 3 = Nearly every day
Item 8.	I avoided places where it would be difficult to get help if I had a seizure. 0 = Not at all 1 = Several days 2 = More than half the days 3 = Nearly every day
Item 9.	I avoided places where people could witness me having a seizure. 0 = Not at all 1 = Several days 2 = More than half the days 3 = Nearly every day
Item 11.	I thought a lot about the possibility of having a seizure. 0 = Not at all 1 = Several days 2 = More than half the days 3 = Nearly every day
Item 16.	I became frightened when I noticed signs or symptoms related to my epilepsy. 0 = Not at all 1 = Several days 2 = More than half the days 3 = Nearly every day
Item 18.	I worried whether I might do something to bring on a seizure. 0 = Not at all 1 = Several days 2 = More than half the days 3 = Nearly every day

Table 3
Pharmacological agents presenting an interest to treat AAS.

First-line drug treatment (in order of preference)	
Citalopram	Initiate at 10 mg/day for one week, then increase at 20 mg/day (target dose); when insufficient resolution after two weeks: possible increase at 40 mg/day (maximum dose)
Sertraline	Initiate at 25 mg/day for one week, then increase at 50 mg (target dose); if necessary, increase by 50 mg/day every week, until 200 mg/day (maximum dose)

Table 4
Pharmacokinetics between ASM and Citalopram, Sertraline [15].

Antidepressants (ADs)	ASMs	Therapeutic measures for ADs
First-line drug treatment		
Citalopram, Sertraline	Powerful inducers: Carbamazepine, phenobarbital, phenytoin, primidone	Slight diminution of Citalopram level. No modification of dosage needed (correction factor = 1.3)
Sertraline	Mild inducers (high doses): Oxcarbazepine, Topiramate, Clobazam, Eslicarbazepine, Felbamate, rufinamide	Strong diminution of Sertraline level. Need to triple the dose for the same effect (correction factor = 3 – 5)
		Possible slight diminution of Sertraline. No systematic modification is needed.
		Systematically check efficacy and tolerance after adding or discontinuing those ASMs

depressive disorders in this patient.

Possible iatrogenic process?

The involvement of side-effects of lamotrigine in anxious symptoms might have been possible [2]. Indeed, Lamotrigine, Levetiracetam and Topiramate are known for their anxiogenic effects[2]. According to the psychiatric interview, there was no clear relationship between increases in dosage and the intensity of anxiety disorders. The triggering factor of anxiety were two seizures: (a) when she was preparing the bath for her daughter and (b) when she was at work (mother-children care home). Besides, Lamotrigine may have contributed to the accentuation of anxiety disorders. But the patient has refused the decrease or discontinuation of Lamotrigine, which could have highlighted the causality of this medication. Since anxiety disorders improved, the patient agreed to start a slow decrease in Lamotrigine.

Available self-rating scales

There is no validated specific scale for anticipatory anxiety of seizure (AAS). The following questions are useful for assessing AAS: “Are you excessively concerned, worried, or anxious about having a seizure?” and “Do you have marked, and persistent fear related to the expression or the consequences of your seizures?” “How would you rate this worry of having a seizure on a scale of 0–10? 10 being the maximum level of worry?”[1]. Alternatively, the items numbered 5, 7, 8, 9, 11, 16 and 18 of the EASI scale [3] could be used to cover this dimension (see Table 2). As we discussed, AAS is often comorbid with various anxiety disorders, and the EASI scale seems to be an efficient assessment tool (Table 3 and Table 4).

Pharmacologic treatment considerations in the treatment of AAS and interictal anxiety disorders

Since no specific recommendations exist for the management of specific anxiety symptoms or disorder in PWE, one approach should base on existing guidelines in general psychiatry that we adapt for PWE [5].

As anticipatory anxiety of seizures (AAS) is similar to the anticipatory anxiety seen in panic disorder [1], we recommend to use molecules efficient in Panic Disorder[6].

Safety for use in epilepsy

First, one should be reminded that the use of psychotropic medications, especially the antidepressants SSRI and anxiolytics, is not associated with a worsening of epilepsy [7]. Therefore, there is no argument to undertreat the anxious disorders of PWE. Anxiety disorders are associated with a greater frequency of seizures, an increased risk of suicide and of having ASM side-effects[8]. Moreover, anxiety disorders are one of the strongest determinants in the impairment of the quality of life in PWE [9]. Secondly, the antidepressants might be associated with a decrease in the frequency of seizures [10,11].

Medications choices to treat interictal anxiety disorders

Optimizing the antiseizure medication (ASM)

As ASM are known to have psychiatric side effects, the clinician should first optimize the treatment, as much as possible, considering the type of epilepsy, the severity of AAS, and the imputation of ASM [2]. Some ASM might have beneficial effects on anxiety and other psychiatric conditions, beneficial such as gabapentin, pregabalin, clobazam, carbamazepine oxcarbazepine, and valproate[2,5]. It is noteworthy that Pregabalin is recommended in general psychiatry for the treatment of certain anxiety disorders [12]. Nonetheless, GABAergic agents have a potential risk of misuse, needing a medical vigilance [13].

First- and second-choice psychotropic medications

According to treatment guidelines for anxiety disorders, antidepressants are the first-line choice: Selective Serotonin Reuptake Inhibitors (SSRIs), or Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) [13]. Benzodiazepines are limited to the treatment of paroxysmal anxiety for a short time [13]. To the best of our knowledge, the reference medications for panic disorder can be considered as powerful agents for reducing anticipatory anxiety by attenuating the anguish of having a future attack. According to the psychiatric practice, we propose two pharmacological agents to treat AAS: Citalopram and sertraline (see Table 1 for prescription guidelines). Besides, those two agents are also efficient against the other types of anxiety in PWE.

For each medication trial, a minimum delay of 6 weeks is needed before concluding to a failed trial[14].

Potential pharmacokinetic and pharmacodynamic interactions

Some ASM are known to be metabolic inducers or inhibitors through liver cytochromes, so that pharmacokinetic and –dynamic interactions are highly frequent with other medications [7,15]. Conversely, some antidepressants also have metabolic properties, that can modify the distribution and effect of ASM [15]. Considering the minimal interactions of sertraline and citalopram on ASM, compared to other SSRIs, these two medications may be the best choices. We proposed a schematic summary of the interactions between ASM, Citalopram and Sertraline (see in Table 2).

Recently developed, Cenobamate (new ASM) needs a special vigilance on pharmacologic interactions, that can be in the two way (inhibition or induction)[16].

It is also noteworthy that ASM can lower the folates level, that might explain a diminished efficacy of antidepressants because folates are involved in the neurotransmitters synthesis[6,17]. Folates can be supplemented at a dosage of 5 mg/day for 3 months. To check the psychotropic treatment and interactions with ASM, one could distinguish two main situations:

- **Absence of efficacy:** perform a plasmatic monitoring of antidepressant and folates levels.
- **Side effects, tolerance:** perform a plasmatic monitoring of antidepressant, ASM, and liver function.

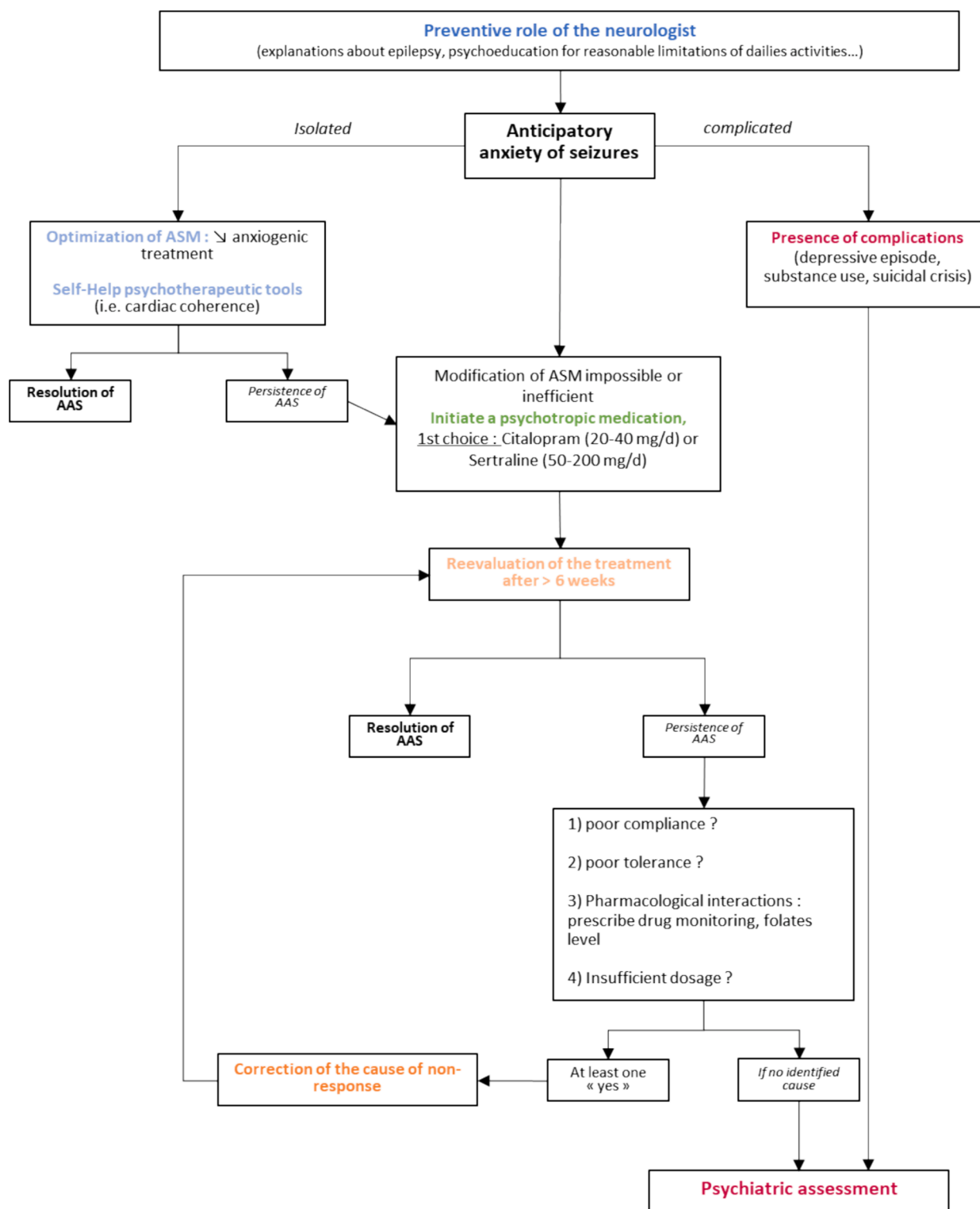


Fig. 2. Schematic recommendations to epileptologists for the treatment of anticipatory anxiety of seizures.

Most common adverse events of the psychotropic medications.

Most of antidepressants adverse events occurred during the initiation, for a short time and are due to anticholinergic effects (nausea, dizziness, dry mouth...) [6,18] This can be corrected by a lower initiation dosage. Nonetheless, some side effects need particular vigilance [6,18]: Citalopram (prolongation of QT interval, that might be used with caution and ECG monitoring when the patient takes Lacosamide); Sertraline (sexual dysfunction, loss of libido). In elderly (over 65 years old),

one should also be careful at the risk of hyponatremia, and bleeding [6,18].

Pharmacological discussion in relation to the clinical case

This patient was prescribed escitalopram. Literature is not clear, for example, whether citalopram is preferable to escitalopram in cases of epilepsy [19–22]. The question of the 20 mg dosage may be raised when the patient is co-prescribed carbamazepine. We did not perform a plasma assay because of the high efficacy. However, we cannot conclude

whether escitalopram or CBT explained the clinical improvement, as both were performed concomitantly. Currently, the dosage of Lamotrigine has been reduced, after which escitalopram withdrawal will be tried.

The role of psychotherapy

For anxiety disorders, the psychological therapy is more effective than pharmacological therapy and should be used as first line when possible [6]. Cognitive-Behavioral Therapy (CBT) relies heavily on exposure to situations that are avoided and exposure to panic sensations. The effect of psychotherapy on anticipatory anxiety is often indirect. It is not possible for AAS to work directly on voluntary exposure to epileptic seizures. But exposure to feared and avoided situations (apart from those which strongly encourage seizures) is necessary. Moreover AAS could be related to the history of previous psychological trauma [23] and to cognitive distortions about the seizure (false beliefs, internal mental biases...). Therefore, psychotherapies that could be useful are CBT and eye movement desensitization and reprocessing (EMDR). But more research is needed. In addition to psychotherapies clinicians should propose self-help tools for the management of anxiety (cardiac coherence exercises available on smartphones, abdominal breathing, safe place, grounding techniques...). Furthermore, there are few evidence for the efficacy of psychotherapies in epileptic seizure control [24].

Preventive role of neurologist on AAS

To our knowledge, there is no specific study on the impact of the neurologist's attitude on the development of an AAS. However, based on our clinical experience, we can offer some advice that neurologists could use during consultations with PWEs.

In PWE with a severe AAS, there are often avoidant behaviors of daily life situations. Because of cognitive biases linked to their anxiety, patients and their relatives quickly overgeneralize the restrictions. According to the type and severity of epilepsy, it is essential for the neurologist to communicate very clearly about what is allowed or not to do, and to formulate explicitly that "*everything else is not contraindicated in the context of your epilepsy*". This limits the risk of misinterpretation and overgeneralization by PWEs and their relatives. The other essential point is to help patients understand the benefit/risk balance of AAS and avoidance. It is important to explain that apprehension of having a seizure is impairing the daily life, more than the seizures themselves.

Referral to psychiatrists?

Since epilepsy is a particular cerebral condition, a systematic psychiatric assessment should be ideally performed to diagnose the type of anxiety and to decide the most suitable therapeutic measures. Because of the variability of anxiety disorders, their assessment is sometimes more complex for neurologists than that of depression. But systematic evaluation by a psychiatrist is not realistic. Thus, we propose two major indications for referral to psychiatrists:

- **AAS with psychiatric severity or complications** (major depressive disorder, substance use disorder, suicidal behaviors, psychotic symptoms)
- **After one failed trial of psychotropic medication** (evaluated at the maximum dose, over 6 weeks, with complete compliance, well tolerated and after excluding a pharmacologic drug interaction)

Summary Recommendations

We proposed schematic recommendations for the treatment of AAS, displayed in Fig. 2. According to the best efficacy and tolerance, and the less risk of drug interactions, the preferred molecules should be Citalopram and Sertraline. In addition, neurologists can have a preventive effect on AAS through the content of their indications during consultations and by making their patients aware of AAS and its consequences on their quality of life.

Ethics approval: Patient gave a written informed consent for scientific use of her medical data after anonymization.

Consent for publication: Written informed consent was obtained from the patient for publication of this case report. A copy of the written

consent is available for review by the Editor-In-Chief of this journal.

Availability of data and materials: The datasets used and/or analysed for the clinical example concerned confidential data and are available only from the corresponding author on reasonable request.

CRedit authorship contribution statement

Coraline Hingray: Writing – review & editing, Writing – original draft, Conceptualization. **Herve Javelot:** Writing – review & editing, Writing – original draft. **Frank Lach:** Writing – review & editing, Writing – original draft. **Alexis Tarrada:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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