

# Panic disorder: from psychopathology to treatment

*Disturbo di panico: dalla psicopatologia alla terapia*

G. Perna\* \*\* \*\*\*

\* Hermanas Hospitalarias, FoRiPsi, Department of Clinical Neurosciences, Villa San Benedetto Menni, Albese con Cassano, Como; \*\* Department of Psychiatry and Behavioral Sciences, Leonard Miller School of Medicine, University of Miami (USA); \*\*\* Department of Psychiatry and Neuropsychology, Maastricht University (the Netherlands)

## Summary

*Panic disorder (PD) is a clinical entity which complexity can be organized in a “march of panic” whose organizing psychopathological principle is represented by the unexpected panic attacks. Panic phenomenology is defined not only by full blown and limited symptoms panic attacks but also by aborted panic attacks and shadows of panic. All together these phenomena are the expression of the psychobiological mechanisms abnormally activated in PD. The target of psychopharmacological treatment should be focused on panic phenomenology while the only effective psychotherapeutic intervention, cognitive behavioral therapy,*

*should correct the cognitive distortions and the avoidant and protective behaviors that limit panic patient’s freedom. A complete therapeutic approach should include also regular aerobic exercise and evidence based breathing therapy. Often the chronicization of PD is the results of mistakes in the diagnostic and therapeutic processes rather than a true treatment resistance.*

## Key words

*Panic disorder • Panic attacks • Drug treatment • SSRI • Psychopathology • CBT*

## 1. Functional psychopathology

### 1.1 Clinical complexity and simplicity in panic disorder

Panic disorder (PD) affect approximately 3-4% of general population, mostly women with an age of onset around 20-25 years<sup>1</sup> and it is associated with a significant worsening quality of life<sup>2,3</sup>. In addition, PD is associated with an high use of health care services<sup>4</sup> and a low productivity due to an increased disability<sup>5</sup> and many days off of work<sup>3</sup>.

The choice of an appropriated treatment involves a correct diagnostic process. The identification of nuclear psychopathological phenomena, as the central organizing clinical elements, and the secondary psychopathological events becomes a key factor of the diagnostic process. Diagnostic and Statistic Manual of Mental Disorder (DSM) IV revision<sup>6</sup> can provide some general guidelines for the diagnostic process, but is still insufficient for a therapeutic program when the aim is a full recovery of a normal life. The clinical picture of PD includes a constellation of mental phenomena that influence negatively patient’s quality of life and his functioning: panic attacks, agoraphobia, anticipatory anxiety, depression, anxiolytics and alcohol abuse and hypochondria. When we organise the described complexity of the clinical picture into the so called “panic march” (Fig. 1), the clinical process become

relatively simple revealing that the core elements are the unexpected panic attacks, while the other psychopathological phenomena are mainly secondary to panic attacks’ appearance.

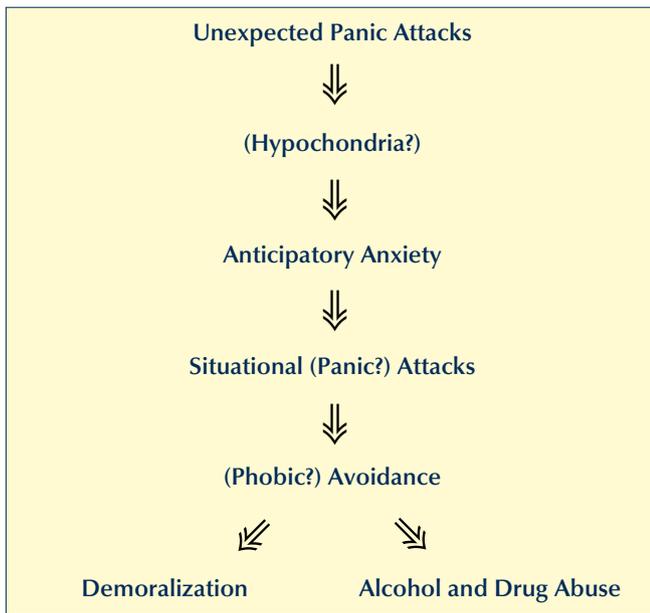
The individual reaction and adaptation to the appearance of unexpected panic attacks is mediated by the psychological and physiological underground on which they will impact. An avoidant personality would lead to development of a severe agoraphobia, vulnerability to obsessive-compulsive spectrum disorders would stimulate hypochondria and so on. It’s important to identify in the unexpected panic attack the “primum movens”. Thus, the pharmacological prevention of all unexpected panic attacks (complete and serious and less severe ones) is the starting point of a complete recovery of normal behaviours, which can be reached with a gradual overcoming of the secondary psychopathological phenomena. The latter are the results of psychological and behavioural mechanisms that patients activate to defend from unexpected panic attacks.

### 1.2 Clinical organizing principles beyond DSM

The central therapeutic action should be focused on the complete prevention of panic attacks’ recurrence. The phenomenology of panic attacks is far from being simple to describe as it is generally supposed. If the unexpected appearance of a strong distress, more physical than men-

## Correspondence

Giampaolo Perna, Department of Clinical Neurosciences, Suore Ospedaliere – Villa San Benedetto Menni, Albese con Cassano (CO), Italy • E-mail: pernagg@tin.it



**FIGURE 1.** "March of panic". The progression of panic disorder. "La marcia del panico". La progressione del disturbo di panico.

tal, without an organic and demonstrable pathology, set down for a panic attack. This phenomenon could be very heterogeneous in the presentation, severity and features. Panic attacks are characterized by its unexpected presentation (PA unexpected) or at least not completely predictable (PA predisposed) while both the intensity, and the number of symptoms are not central in their clinical definition. Panic attacks are the expression of the basic pathological mechanism activity underlying PD. Beyond classical panic attacks, there are two other phenomenology events, harder to recognize, that are still the expression of the basic pathological mechanism: we can call them "abortion" of panic attack or "panic attack shadow". The first one indicates the sensation of an imminent appearance of a panic attack with no clinical manifestation, the second one, even finer, is the expression of the instability of the homeostatic system supposed to be the biological roots underlying the vulnerability to panic attacks and that manifest itself with abnormal somatic sensations, sub continuous, mainly involving cardiac, respiratory and postural systems that maintain a state of somatic alarm. It is not easy to distinguish if this last phenomenon is the expression of heightened attention to the soma due to the activation of the emotional memory of the attacks, or if it is the expression of activation of somatic alarm system still dysfunctional. Finally it is very important to distinguish panic attacks from acute anticipatory anxiety (situational panic attacks); the latter is a secondary response to unexpected panic and they should not be considered the main target of drug treatment. The identification of panic attacks and

their soften expressions and the ability to distinguish them from acute anxiety phenomena or fear are crucial for a correct comprehension of PD and evaluation of the efficacy of the therapeutic intervention <sup>7</sup>. Only when all the psychopathological expressions of panic vulnerability is blocked and prevented, than the goal of an anti-panic treatment are reached. This will allow removing all patients' defences and leading to a complete wellbeing.

The other two clinical phenomena that define PD and are the expression of defences' reaction to unexpected panic attacks recurrence are anticipatory anxiety and agoraphobia.

While the severity of anticipatory anxiety is variable from patient to patient since it is modulated by the previous experiences and temperament, its appearance is due to the recurrence of panic attacks in all their clinical expressions. To obtain the complete remission of anticipatory anxiety, panic disappearance is required. Drug treatment for anticipatory anxiety should be temporary and limited to the acute phases.

Agoraphobia is the third clinical phenomenon featuring PD and, in the context of this disorder, should be considered a physiological defensive response to the recurrence of panic attacks, thus fear reaction rather than a true phobia.

Agoraphobic avoidance is a behaviour that rises from the activation of defensive strategies against panic attacks and can be influenced by temperament, organic features and emotional experiences. The latter factors, however, should not be considered causes, but intensity and strength agoraphobia's modulators. If so, once again panic disappearance is required to get over the avoidant behaviours of agoraphobia.

Between organic factors that can influence the severity and persistence of agoraphobia, the balance system plays an important role. There is a significant association between the severity of agoraphobia and sub-clinical abnormalities in the balance system, especially when visual information is lacking <sup>9</sup>. Some studies suggest the possibility to improve the function of postural system with drugs treatment or with specific rehabilitation program <sup>10</sup>. Other studies suggest the validity of new pharmacological treatments for the potentiation of behavioural systematic desensitization <sup>11</sup>. Agoraphobia is a complex phenomenon, which most of the time is a defensive response to panic attacks, so we need to keep in mind that the first intervention must be addressed to the blockade of the recurrence of panic attacks. When we talk about agoraphobia we can't forget protective behaviours, such as dependence from a phobic partner, that persist until panic attacks are gone.

In order to complete clinical picture of PD it is important to underline the presence of hypochondria, especially when a obsessive compulsive spectrum is present in the

background, depression and alcohol or benzodiazepine abuse (BDZ), usually used as self therapy against panic attacks. Most of the time, all these phenomenological events appear after the onset of panic attacks as its logical consequences, their resolution once again depends from panic attacks disappearance. Finally, we can't forget the relationship between bipolar disorders and PD that have a strong influence on the choice of the appropriate treatment (deepened in another article of this volume). The hardest thing for a clinician is to correctly distinguish between a physiological increase of mood and positive and explorative behaviours during the remission phase of PD and the activation of pathological mechanism of bipolar vulnerability. Whenever there will be a doubt, a longitudinal observation of patients' behaviours and mental state will become a precious source of information to understand this relationship.

## 2. "Evidence based" pharmacological treatments

Effective drugs for PD includes selective inhibitors of serotonin reuptake (SSRI), inhibitory of serotonin and noradrenaline reuptake (SNRI), tricyclic antidepressants (TCA) and high potency BDZ. Despite irreversible monoamine oxidase inhibitors (MAOI) are effective anti panic agent, their use is limited from adverse reactions associated and from dietetics restrictions. SSRI mainly modulate serotonergic system, SNRI and some TCA modulate both serotonergic and noradrenergic ones and BDZ modulate the  $\gamma$  aminobutyric acid system (GABA). Even if their mechanisms of action are still uncertain, the efficacy of these anti panic drugs could be mediated by their effects on different cerebral functions potentially involved in the physiopathology of PD, like the hypersensitivity to suffocative stimuli or a wider dysfunction of brain homeostatic mechanisms<sup>13 14</sup>, an abnormally sensitive fear system<sup>15</sup> and interoceptive/exteroceptive conditioning processes<sup>16</sup>.

### 2.1 Selective serotonin reuptake inhibitors

SSRI are the first choice drugs for the pharmacological treatment of PD, with or without agoraphobia, either for the acute treatment than for the long term one, given the most favourable balance between efficacy and side effects compared to others drugs available<sup>17 18</sup>. To date, six SSRI are available: paroxetine, sertraline, citalopram, escitalopram, fluoxetine, fluvoxamine. Most of them showed the ability to reduce behavioural reactivity to the inhalation of high dose carbon dioxide (CO<sub>2</sub>), which is considered a marker of vulnerability to panic, in patients with PD. Recent guidelines suggest no differences in the anti panic effectiveness of the different SSRI available,

while there could be some differences in their half life, side effects profile and interaction with other drugs. Some experimental data, however, have shown that one month treatment with fluvoxamine have led to worse results in patients with a respiratory subtype panic compared to paroxetine, sertraline, imipramine and clomipramine<sup>19</sup> and that two months of treatment with paroxetine showed a trend to be more effective in the reduction of unexpected panic attacks than citalopram<sup>20</sup>. These data suggest that there could be differences in clinical anti panic properties among different SSRI due to differences into pharmacodynamic profiles of these drugs. SSRI have a more favourable side effects' profile than TCA, they have safer cardiovascular profile and they show a lower risk of overdose. They are not associated with the development of tolerance or physical addiction, even if an abrupt withdrawal could lead to a withdrawal syndrome, especially with paroxetine, which, however, can be minimized with a progressive reduction of the dose during several weeks, possibly using drop formulation. Starting doses should be lower than the therapeutic ones, in order to support the tolerance in the first phase of treatment<sup>21</sup>. Usually, the appearance of therapeutic effects need at least 2 to 4 weeks. SSRI have common side effects that include headache, nausea, sleepiness, sexual dysfunction and weight gain, some of them are transitory, some others continue for the entire treatment even if each SSRI have a different side effects profile. Finally some SSRI have an inhibitory effect on enzymatic system of cytochrome p450 and thus might be associated with pharmacological interactions potentially dangerous. Despite SSRI have represented a central progress in the pharmacotherapy of PD, many questions are still open, as not responders, the delay onset of their therapeutic action and side effects profiles.

### 2.2 Selective serotonin and noradrenaline reuptake inhibitors

Venlafaxine extended release is the only drug of this category that has been recommended for PD since to date there are no systematic data available supporting the use of other SNRI. Venlafaxine showed anti panic properties both in placebo-controlled randomized studies and comparative studies with paroxetine<sup>22 23</sup> and was able to decrease CO<sub>2</sub> hyperreactivity in patients with PD<sup>24</sup>. Venlafaxine is usually well tolerated with an efficacy and a side effects profile comparable to those of SSRI, even if a small group of individuals could develop arterial hypertension, an effect dose dependent and related to the immediate release formulation.

### 2.3 Tricyclic antidepressants

Clinical studies supported the efficacy of clomipramine in PD, comparable to SSRI's one<sup>25</sup>, and laboratory stud-

ies showed a decrease of CO<sub>2</sub> hyperreactivity in patients with PD<sup>26</sup>. Imipramine seems to have weaker anti panic properties than clomipramine and SSRI, in particular in the respiratory subtype<sup>19</sup>. TCA are considered a second choice treatment for their less tolerability and safety profile compared to SSRI. TCA could induce several side effects, due to their antagonistic effects on muscarinic,  $\alpha_1$  adrenergic e histaminergic receptors and so they shouldn't be prescribed to patient with prostate gland hypertrophy, glaucoma, cardiac conduction abnormalities.

TCA with a more noradrenergic profile, like desipramine and maprotiline, are the less effective in the treatment of patients with PD<sup>27</sup>, supporting the importance of serotonergic system modulation in the therapy.

### 2.4 Benzodiazepines

High potency BDZ like clonazepam and alprazolam, the latter now available in an extended release formulation, are molecules effective in the treatment of PD<sup>28,29</sup>. Their fast action, high tolerability and patients' acceptability probably are the reason of the wider use in the treatment of PD. Despite some studies suggest that BDZ are safe and well tolerated in the long term treatment<sup>30</sup>, they present some disadvantages compared to the other anti panic drugs and international guidelines recommend a parsimonious use for their side effects like sleepiness, weakness, cognitive and memory's disturbances, high risk of tolerance, addiction and abuse.

BDZ combined with SSRI in the first week of treatment seem to speed up the therapeutic response compare to the SSRI alone<sup>31,32</sup> and relieve the initial increase of anxiety, even if there is not a real advantage after the first weeks of treatment.

SSRI, SNRI e TCA should be preferred to BDZ as monotherapy for patients with concomitant depression or drug abuse disorders<sup>21</sup>. Finally, some data show that patients with a combined therapy with CBT and BDZ, afterwards discontinue treatment with BDZ, have a loss of efficacy compare to CBT and placebo, probably due to a BDZ interference with fear extinction processes, suggesting caution in their use during cognitive behavioural therapy<sup>32</sup>.

### 2.5 Other molecules

Other drugs, for example mirtazapine and reboxetine, with less empirical support, are not recommended as standard treatment for PD, but they could be considered for those patients with PD who failed with traditional treatments. Some studies seem to suggest a potential use of atypical antipsychotic for the traditional anti panic therapies, but to date there are not enough experimental evidences to recommend them<sup>21,33,34</sup>.

## 3. Clinical psychopharmacology of panic disorder

The first fundamental step toward the understanding of the role of panic attacks in this disorder is an accurate anamnesis that aims to organize the clinical phenomena described by the patient into the "march of panic". Once the clinical picture becomes clear it would be necessary to exclude any possible medical-related (ex. hyperthyroidism, heart rhythm disorders) or pharmacological causes (ex. theophyllines, beta-blockers).

When the diagnosis has been confirmed, the evaluation process for the most suitable pharmacological treatment can begin. It is always important to keep in mind that the clinical outcome of a pharmacological treatment would depend on both the psychoactive molecule and the substrate, here represented by the patient with his age, overall medical conditions and his relational and emotional state. The choice of the molecule will find in the anti panic potency an important but not sufficient element: are also essential, needs of the person who receives it and his life: an account is to give a molecule with significant sexual side effects to a young girl, and another thing is to treat an elderly person of 75 years with a stable relational life; as well as treating a person with significant medical comorbidities is very different from treat a healthy young person. In all these cases the pharmacological choice may not be the same, but must take into account the balance between costs and benefits. To eliminate the symptoms of PD at the cost of the complete inhibition of sex life or a substantial increase in weight may worsen rather than improve the quality of life of a patient. That said, integrating the results of experimental studies with clinical experience, we try to give some comparative judgment. As for the anti panic potency, it is possible to classify the molecules according to the scheme described in the table below (Table I). Although insufficient experimental evidence related to the scarcity of comparative studies between molecules, the rationale for the greater efficacy of paroxetine and clomipramine reside in the modulation combined on serotonergic and cholinergic systems. Another key element in choosing the most appropriate drug therapy for a patient with PD is the assessment of side effects, potential toxicity and interactions with the cytochromes. The anti panic molecules have very different profiles about that (Table II). The personalization of the anti panic treatment must combine the anti panic potency with the safety and side effects profile, in order to optimize the well being of the patient. Once you have chosen the molecule, it will be essential reach the minimum therapeutic dose (paroxetine 20 mg, escitalopram 10 mg, sertraline 50 mg, clomipramine 37,5 mg) gradually in a max of 2 weeks, to evaluate whether to increase about after 6-8 weeks the dose depending on clinical response, which has as its

primary aim the disappearance of panic attacks. For each increase, the clinical response should be assessed carefully and the dose increased until the complete disappearance of the panic attacks in all its clinical presentations (also the shadow of panic). With the reduction of the attacks, the expectation is a gradual decrease in anticipatory anxiety, agoraphobia and all the complications of panic, aided by a cognitive-behavioral therapy. The persistence of panic attacks in all its forms (complete, partial, abortion or shadow) after 6 months, should advise a change of the choice of the panic molecule. Similarly, the persistence of anticipatory anxiety or agoraphobia, also light, especially after a well done cognitive-behavioral therapy, must raise the suspicion of a persistence of panic and for this reason recommend a re-evaluation of drug therapy.

Despite the absence of direct experimental evidence, the clinical experience combined with a psychobiological rationale, can give some more specific indication on the choice of molecule in case of insufficient response with the molecule chosen as the initial therapy (Table III).

**TABLE I.**

Anti panic potency and psychoactive molecules. *Molecole psicoattive e potenza antipanic.*

Anti panic potency	Psychoactive molecules
Excellent	Clomipramine, paroxetine
Very good	Sertraline, escitalopram, venlafaxine, imipramine
Good	Citalopram, alprazolam, clonazepam
Modest	Fluvoxamine, fluoxetine, duloxetine

**TABLE II.**

Adverse effects of antipanic molecules. *Effetti secondari sfavorevoli delle molecole antipanic.*

Side effects, toxicity e cytochromes interference	Psychoactive molecules
Weigh gain, sexual dysfunctions	Clomipramine, paroxetine, citalopram, imipramine
Potential cardiovascular abnormalities	Clomipramine, imipramine, venlafaxine, duloxetine, citalopram, escitalopram
Cytochromes interference	Fluvoxamine, fluoxetine
Sedation, tolerance e dependence	Alprazolam, clonazepam

**TABLE III.**

Practical clinical tips in the choice of antipanic molecules. *Suggerimenti clinici nella scelta delle molecole antipanic.*

Clinical feature	Psychoactive molecules
Severe agoraphobia with postural symptoms (instability and dizziness)	Sertraline, clomipramine
Obesity, dyslipidemia	Escitalopram, sertralina
Comorbidity with generalized anxiety disorder	Venlafaxine, duloxetine
Irritable bowel syndrome, panic attacks with diarrhea	Clomipramine, imipramine

Although it has a different pharmacodynamic profile compared to paroxetine, the sertraline could be actually the SSRI that looks more like in functional terms, thanks to the ability, even if weak, to block the reuptake of dopamine (DA)<sup>35</sup>. Indeed, people with DP could be characterized by a cholinergic receptor up-regulation that would make the system more sensitive to fluctuations of phasic stimulation of these receptors<sup>36</sup>, able to generate respiratory symptoms, cardiac and vestibular between and during panic attacks, providing a rational explanation of the excellent anti panic properties of the drugs with antimuscarinic properties such as paroxetine and clomipramine. Under the functional antagonism DA/ACh at the ventral brainstem level, the increasing of the dopaminergic tone may decrease the responsiveness of the cholinergic system, reducing the frequency and intensity of symptoms caused by its phasic fluctuations. The interrelationship between these two systems is supported by scientific literature<sup>37-39</sup>.

The importance of the dopaminergic in postural stabilization system (think at the use of the tiethylperazina and the levosulpiride indication of the treatment of vertigo) suggests that in agoraphobic patients who report frequent unsteadiness and dizziness are preferred serotonergic molecules with dopamine properties as the sertraline and clomipramine. In the event of significant gastrointestinal symptoms (irritable bowel syndrome, diarrhea) imipramine and clomipramine may be useful because of their relevant anticholinergic effect. If, however, there are aesthetic needs and strong medical contraindications to a potential increase in weight, will be preferred molecules without an antihistamine and antimuscarinic properties,

such as escitalopram and sertraline. SNRIs (venlafaxine and duloxetine) are to be preferred, in those cases where there is a disproportion between generalized anxiety symptoms, panic phenomenology in favor of the first, as often happens in chronic PD in which the nuclear elements (unexpected attacks) are extinct.

After achieving the complete remission of symptoms of PD, with total disappearance of panic attacks and their "shadows" (keeping in consideration the cognitive and emotional tendency to overestimate physiological somatic sensations) and the complete recovery of autonomy, the

therapy should be maintained for at least 12-24 months and then, in the absence of pathological signs, should be tapered off over 2-6 months.

With to the drug therapy, the cognitive-behavioral psychotherapy will assume a central role, able to correct the cognitive distortions and the avoidant and protective behaviors that limit panic patient's freedom. Another crucial aspect of the therapeutic program is psychoeducation that should be made before that beginning of the treatment explaining to the patients the origin of the disorder, its progression (march of panic) and both the pharmacological and non-pharmacological treatment objectives and the follow up.

Once the treatment is stopped, the patient must be followed in the next year with regular visits every 3-4 months and then stop the visits. If the patient relapses repeatedly with significant symptoms of PD, should be observed the opportunity of a low-dose maintenance therapy.

#### 4. Evidence of psychotherapies based on the treatment of panic disorder

Till today, the cognitive-behavioral psychotherapy (CBT) is the only one that have sufficient data to justify its use in the treatment of PD with or without agoraphobia<sup>18 21 40</sup> with evidences of an efficacy in monotherapy overlapping with that of SSRIs. The combination of psychopharmacological and cognitive behavioral therapy today is the intervention that provides a better clinical outcome in the short and long term<sup>41 42</sup>. While the drug therapy has a specific role blocking the occurrence of spontaneous panic attacks, the central role of cognitive behavioral psychotherapy is the recovery of behavioral autonomy and the restructure of dysfunctional thoughts that happens often as a result of unexpected panic attacks .

#### 5. Does exist the panic-resistant? Mistakes to avoid

An analysis of the literature shows that 20-40% of patients treated pharmacologically are unresponsive to therapies, similarly to the 30-40% of patients treated with cognitive-behavioral therapy. Even the integrated therapies are not able to reduce this percentage significantly<sup>41</sup>. Studies on predictors of not response gave little consistent results, identifying in the disease duration, disease severity, comorbidity with psychiatric disorders and personality, the presence of severe agoraphobia and blood phobia, some negative elements. At follow-up data would seem even more daunting given that 25-50% of patients relapse within 6 months after discontinuation of drug treatment and the percentage of patients in clinical remission varies from 12% to 38% in follow-up studies at 3-5 years. Add to it that 40-60% of patients after a follow up of 4-6 years

shows a subclinical symptomatology attenuated and 20-30% a clinical symptomatology identical to the initial<sup>21</sup>. From this picture it seems that PD may be considered a chronic relapsing disease. The clinical reality shows a more encouraging picture with many patients that go toward a complete remission and a good percentage that shows stability of the remission obtained. If you do not get optimal results in the treatment of PD is more likely to be due to errors in the clinical approach, rather than a real patient's resistance. Errors can occur both in the diagnostic phase (Table IV) that in the pharmacological therapy phase (Table V), which during the psychotherapeutic phase (Table VI).

The most common mistake in psychopharmacological intervention of PD without psychiatric comorbidity (not to be confused with the complications described above), is to think that a drug is like another one or a combination of drugs can be the best thing. We have already discussed

**TABLE IV.**  
Most common diagnostic errors. *Errori diagnostici più comuni.*

Frame PD as a "masked depression"
Ascribe PD to a personality disorder or to interpersonal/childhood conflicts
Forget the "march of panic": several social phobias, hypochondrias, depressions, alcohol and BDZ abuses might be secondary complications of PD and thus panic should be the primary focus of the clinical treatment.
Differential diagnostic mistakes with attacks due to medical diseases or pharmacological compounds

**TABLE V.**  
Therapeutic mistakes in pharmacological interventions. *Errori terapeutici nell'intervento farmacologico.*

Wrong choice of the psychotropic drug
Use of cocktails of psychotropic drugs
Avoiding the increase of doses until the full remission of panic attacks, including panic shadow.
Taper off drug treatment before at least one year of full remission

**TABLE VI.**  
Mistakes in psychotherapeutic intervention. *Errori nell'intervento psicoterapeutico.*

Wrong choice of the type of psychotherapy (only CBT effective)
CBT not correctly carried on
CBT as monotherapy while unexpected panic attacks still persist
Systemic desensitization while panic phenomena still active
Use of BDZ during exposure to phobic stimuli

the first point, we can dwell on the second. BDZ should be avoided in the long term, although in the first days of treatment with serotonergic drugs could be useful to join them to contrast worsening of anxiety but should be suspended gradually after a couple of weeks.

Beyond this combination drug (SSRI + BBZ), the use of other combinations of drugs in the first phase of care, has no scientific foundation. The cocktails should be avoided. Similarly, also in patients suffering from a PD without other concomitant psychiatric disorders, the use of antipsychotics, typical and atypical, tricyclics different from imipramine and clomipramine, mood stabilizers, anticonvulsants, it is not enough scientifically justified. Only when the correct application (congruous doses and time), of evidence-based pharmacological therapies does not give significant results, then the clinician will be authorized to use his clinical "art" to administer or add psychoactive molecules without clear evidence of effectiveness. With regard to psychotherapy, including common mistakes that can undermine the effectiveness of treatment of PD, the coarsest is the choice of the type of psychotherapy to integrate. Once again it is worth to remember that "classical" cognitive behavioral psychotherapy is the only one with sufficient scientific evidence of effectiveness, the use of any other approach is not justified<sup>18 21 40</sup>. Not infrequently the CBT is not performed properly by following the scientifically validated protocols. As noted above, the persistence of panic phenomena (unexpected attack, predisposed, aborted and shadow of panic) will make difficult and probably insufficient the psychotherapeutic intervention. If unresolved, panic attacks will tend to maintain all secondary dysfunctional psychological phenomena.

The use of BDZ during exposure and in the course of CBT should be avoided for their ability to interfere with the extinction of the response and so with the deconditioning to the phobic stimulus<sup>43</sup>.

## 6. Is the pharmacologic therapy sufficient in the panic disorders?

In some cases, the anti-panic medication, applied correctly with its capacity to block the recurrence of panic attacks and to promote the disappearance of attenuated symptoms, is sufficient to start the cognitive and behavioral remodeling that will lead to the recovery of the autonomy and emotional and behavioral freedom. The patient, in these cases, is able of relearn normal behaviors and rebalance cognitive interpretation of somatic sensations once removed "pathogenic noxa," unexpected panic attacks, which started the progression of PD (march of panic) with its negative consequences on the performance and quality of life. In many cases, however, blocking the recurrence of panic attacks in all its forms, ob-

tained pharmacologically, does not allow the beginning of psychological mechanisms able to restore normalcy. In these cases it is important that the patient should follow a cognitive behavioral therapy and it is crucial that the program should be focused on classical behavioral desensitization and cognitive restructuring.

Patients with PD, as discussed previously, show an not normal regulation of different physiological functions, including irregularities in their basal respiratory pattern, reduced heart rate variability (HRV) and an altered functionality of the postural system<sup>8-10</sup>. Patients with PD also have a reduced cardiovascular fitness<sup>44</sup>. Therefore, waiting for a more comprehensive understanding of the pathophysiological mechanisms of PD and then define interventions more specific and central, we must emphasize the need for a holistic approach to the therapy of PD that alongside the integrated pharmacologic treatment and cognitive-behavioral approach, should include somatic therapies starting to have a strong experimental evidence of effectiveness. These therapies are aimed to correct the above mentioned trait homeostatic abnormalities in patients with PD, possibly representing the basic pathophysiological mechanism, which if are not corrected perpetrate and sustain the disorder. Among these we recommend aerobic exercise (aerobic exercise for at least 30 minutes 3 times a week)<sup>45 46</sup>, respiratory therapy (only for protocols with experimental evidences of effectiveness)<sup>47-49</sup>, psycho-vestibular rehabilitation<sup>10 50</sup> and cardiobiofeedback<sup>51</sup>, the latter two very promising although still to be studied in PD.

## 7. Future prospects in psychopharmacology of panic disorder

As previously described in epidemiological studies a high proportion of patients (20-40%) does not respond to drug therapy and an important percentage (25-50%) falls within six months of stopping therapy while up to 40-50% continue to have residual symptoms at 3-6 years or, worse, the disorder in a full 20-30% of cases<sup>21 41</sup>. Even supposing that some of these data can be explained by errors in the treatment of patients, they indicate the need to develop new approaches, expanding the range of molecules anti-panic available to increase the percentage of responders and prevent chronicity of the disorder.

The ongoing pharmacological research for the treatment of PD is focusing on two main areas: 1) development of new compounds with new mechanisms of action; 2) the potential effectiveness of existing drugs already used to treat other psychiatric disorders, especially atypical antipsychotics and anticonvulsants<sup>34 52</sup>. The metabotropic glutamate receptor agonists of type II may be helpful in controlling panic attacks with a favorable side effect profile even if the results are still mixed on their effective-

ness<sup>53,54</sup>. The D-cycloserine, however, a partial agonist of the NMDA receptor, is emerging as a new pharmacological strategy to increase the retention of therapeutic acquisition and extinction of fear based on the exposure provided by CBT in patients with PD and agoraphobia. In actual fact, rather than improve the outcome of these patients, it seems that D-cycloserine accelerate the reduction of symptoms<sup>11</sup>. The levetiracetam and atypical antipsychotics, drugs already approved for other indications, are under study in PD but there are no data available on their ability to block laboratory induced panic attacks and most of the clinical trials included patients with other psychiatric conditions comorbid with PD<sup>34</sup>. These new options may offer some advantages for their side effect profile, but further studies are needed to understand their specific anti-panic properties and their impact on the treatment of PD. Potential new pharmacological strategies may arise from the study of other systems involved in the PD, as the cholinergic system in particular, but also of the opioid and orexin systems<sup>34</sup>. However, currently, no psychopharmacological studies are available. Regarding the cholinergic system, was proposed a model of PD centered on the cholinergic system to explain the increased sensitivity to stimuli suffocate, avoidance and fear conditioning<sup>36</sup>.

The physiological response to hypercapnia in mammals and humans, with the increase in ventilatory rate, arousal and vigilance, is regulated in part by cholinergic mechanisms, with muscarinic receptors in the ventral spinal cord playing an important role<sup>55</sup>.

According to this idea, the greater clinical efficacy of clomipramine and paroxetine compared with fluvoxamine in patients with a respiratory subtype of PD and the trend toward a higher efficacy of paroxetine than citalopram on unexpected panic attacks<sup>20,23</sup>, could be linked to anti-cholinergic properties of these molecules. The use of antimuscarinic drugs could be a potential strategy for the prevention of unexpected panic attacks in PD. The central element of this model could be reduced cholinergic drive, of which the upregulation/increased receptor sensitivity, responsible for the marked sensitivity to suffocative stimuli, would be a direct consequence. In principle, a positive modulation of cholinergic drive, possibly deficient in PD, would operate on a series of trait abnormalities linked in different ways to the cholinergic system (respiratory irregularities and CO<sub>2</sub> hypersensitivity, heart rate variability, balance system abnormal reactivity) and might correct the increased receptor sensitivity. This model would explain the apparent confusion in the cause-effect relationship between cigarette smoking and PD<sup>56</sup>. According to this view, smoke would bring with it a causal factor (CO<sub>2</sub>) and a factor potentially therapeutic (the cholinergic agonist nicotine). To date, however, this road has not yet been adequately explored. Finally one must not forget the possi-

bility that the development of pharmacogenetics, currently the subject of extensive study in the treatment of depressive disorder, may provide a valuable tool in the hands of the clinician for individualization of drug treatment as suggested by the evidence of an association between clinical response and genetic polymorphisms that modulate the expression of the serotonin transporter in a sample of patients treated with paroxetine<sup>57</sup>.

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### Conflicts of interest

Giampaolo Perna did not receive any grant.

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