ANTIDEPRESSANTS AND PANIC DISORDER

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Abstract

Several pharmacological approaches showed efficacy for the treatment of patients with panic disorder (PD). However, current guidelines do not provide information about the relative benefit of each pharmacological compound over the others and about how an optimal treatment for each individual patient could be achieved. The aim of the present article is therefore to review available evidence focusing on comparative studies of antidepressants currently used for the treatment of PD. Main findings suggest that selective serotonin reuptake inhibitors (SSRIs) and the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine should be considered as first line agents for the treatment of PD patients because their clinical efficacy is as high as those observed with other classes of antidepressants such as triciclycs but they are associated with a significantly lower likelihood of side effects. Furthermore, some differences could exist among reviewed drugs such that venlafaxine 225 mg could have some advantages over paroxetine 40 mg for the reduction of several anxiety measures, fluoxetine and escitalopram could be associated with a faster onset of action as compared with citalopram and, overall, serotonergic drugs such as paroxetine and citalapram could be more effective than noradrenergic drugs such as reboxetine and maprotiline. On the basis of reviewed data, however, the extent to which other antidepressants vary in terms of efficacy and acceptability is unclear. Because the understanding of which drug could be best tailored to the needs of each individual patient is crucial for improving treatment outcomes of PD patients, further systematic research in this direction is needed.

Key words: panic disorder, anxiety, SSRIs, venlafaxine

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Introduction

Panic Disorder (PD) is a chronic and severe anxiety disorder that is characterized by the presence of recurrent panic attacks and persistent worry about future panic attacks and their consequences (American Psychiatric Association 1994). About 1% to 5% of the general population is estimated to experience PD at some point of life and its prevalence is twice as high among women as among men (Eaton et al. 1994, Goodwin et al. 2005, Kessler et al. 2006, Weissman et al. 1997, Wittchen et al. 1992). Furthermore, PD causes considerable costs for both individuals and society, as shown by increased use of healthcare, absenteeism and reduced workplace productivity (Konnopka et al. 2009).

PD frequently occurs in comorbidity with other psychiatric disorders. Indeed, about 80% of subjects with PD have a comorbid psychiatric diagnosis (Olfson et al. 1997), being major depression the most common comorbid condition (Roy-Byrne et al. 2000, Weissman et al. 1997). A recent study has found that subjects with past-year PD were about 10 times more likely to have comorbid depression (Bystritsky et al. 2010). Other psychiatric disorders such as bipolar disorder, psychosis, post-traumatic stress disorder and generalized anxiety disorder have been consistently associated with PD as well (Bystritsky et al. 2010, Goisman et al. 1995, Goodwin and Hoven 2002, Lepola et al. 1996). PD is also associated with drug abuse, in particular alcohol abuse, probably because PD patients use drugs to self-medicate or they may develop PD as a consequence of drug ingestion or withdrawal (Bystritsky et al. 2010). Additionally, PD has been associated with a higher likelihood of suicidal attempts as compared with the general populations, especially when it occurs along with major depression (Olfson et al. 2000, Vickers and McNally 2004). Note, however, that other studies have underscored that PD patients could be at increased risk of suicide, even after adjustment for affective comorbidity and other suicide factors (Sareen et al. 2005).

Both biological and environmental factors are thought to play a significant role into the development of PD. On the one hand, the median risk of PD is eight

times more likely in first–degree relatives of probands with PD as compared with relatives of control subjects (Knowles and Weissman 1995) on the other, the majority of PD patients report life stressors during the previous 12 months (Roy-Byrne et al. 1986). Accordingly, it has been hypothesized that stressful life events probably contribute to the timing of onset as well as to the maintenance of the disorder (Roy-Byrne et al. 1986, Watanabe et al. 2005). Overall, such findings emphasize the need for a prompt recognition of PD, possibly as soon as the symptoms emerge, and for effective pharmacological treatments so as to reduce the burden related to such disorder for both affected individuals and the society.

Neurobiology of panic disorder

Panic attacks are acute fear reactions to internal or external stimuli that occur in subjects with abnormally sensitive fear networks (Gorman et al. 2000). The amygdala is the central area of fear information processing, which mediates incoming stimuli from environment and stored experiences and stimulates various brainstem areas responsible for key panic symptoms (Gorman et al. 2000). A deficiency in the coordination of stimuli from the cortex and brainstem could lead to an abnormal activation of the amygdala, that, in turn, could lead to an abnormal behavioural, autonomic and neuro-endocrine stimulation (Garakani et al. 2006).

Several interacting neurotransmitter systems also appear to be involved in brain circuitries associated with PD, including serotonin (5-HT), norepinephrine (NE) and γ-aminobutiric acid (GABA) (Gorman et al. 2000). Currently, there are two opposite hypotheses aimed at explaining panic symptoms within the context of a serotonergic dysfunction: 5-HT deficit or under-activity and 5-HT excess or over-activity. The former theory proposes that, in specific brain regions such as the dorsal periaqueductal gray, 5-HT has a restraining effect on panic behaviour and a 5-HT deficit may trigger panic. The latter one suggests that PD patients either have an increased level of 5-HT release or hypersensitivity in postsynaptic 5-HT receptors (Maron and Shlik 2006). Regardless of whether PD is caused by a deficit rather than by an excess of serotonin release or sensitivity, additional support for the proposed involvement of serotonin derives from evidence about the efficacy in the treatment of PD of antidepressants that modulate serotonergic neurotransmission, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (Dell'Osso et al. 2010, Mochcovitch and Nardi, 2010). Among other neurotransmitters involved in the pathophysiology of PD, significant attention has also been given to NE (Gorman et al. 2000, Johnson et al. 1995). Indeed, the locus coeruleus, which contains the highest concentration of NE cell bodies in the brain, is significantly involved in the mediation of fear and anxiety responses (Coplan and Lydiard 1998). Also, pertaining to GABA, there is considerable evidence that dysfunction of GABA(a) receptors and/or deregulation of GABA concentrations in the central nervous system play a role in the pathophysiology of PD (Martin et al.

2009). Benzodiazepines and anticonvulsant drugs may, therefore, have anti-panic effects through the reduction of neuronal excitability in limbic structures, mediated by GABA(a) receptors (Bailey et al. 2009, Pande et al. 2000). However, current evidence about the involvement of such neurotransmitters is far less established as compared with evidence regarding serotonin.

Critical issues related to the treatment of Panic Disorder

Because PD is associated with a significant burden in terms of quality of life, functioning, and economic costs, a prompt recognition and an adequate treatment of this disorder is highly needed. Indeed, the longer PD patients remain without treatment, the worse the prognosis will be (Kasper and Resinger 2001). However, the quality of primary care given to patients with PD is far from being optimal. As an example, PD is often under-recognized and under-treated in primary care setting (Ormel et al. 1991, Roy-Byrne et al. 1999, Stein et al. 2004, Young et al. 2001). This probably happens because PD patients typically present with somatic and medical complaints and have a poor ability to recognize the anxious nature of panic-agoraphobic symptoms (Barsky et al. 1999). Similarly, physicians often focus on physical symptoms and do not investigate the presence of an anxious state (Roy-Byrne et al. 2005b).

In addition, subjects with PD may have an overall dramatically lower perceived need for treatment as compared with patients suffering from other psychiatric disorders (Mojtabai et al. 2002). Moreover, because of the intrinsic nature of this illness, many PD patients are worried about treatment. Indeed they think they could become addicted to drugs and they are concerned about possible adverse effects of drugs. Therefore, education and support should be basic component of the psychiatric management of PD. Furthermore, the development of an optimal therapeutic plan for each individual patient should include consideration of patient's preferences, with particular attention to the risks and benefits of each therapeutic intervention (American Psychiatric Association 2009, Eisenthal et al. 1979, Roy-Byrne et al. 2005a).

Therapeutic approaches for panic disorder

The goal of PD treatment is to reduce or eliminate panic attacks, avoidance behaviour, anticipatory anxiety and concomitant comorbidities. In addition, because PD is a chronic and recurrent illness, patients should achieve a complete and sustained remission before discontinuation of treatment is considered (American Psychiatric Association 2009, Ballenger et al. 1998a). After discontinuation or reduction of the dosage of drug treatment, many patients may experience relapses, even after successful therapy (Keller et al. 1994, Noyes et al. 1993). Some data have revealed that the most important critical factor that predicts relapse is the level of clinical remission obtained at the end of the therapy. In particular, if there are residual anxious symptoms, especially phobic symptoms, treatment should be

continued (Mavissakalian and Perel 2002, Perugi et al. 2007)

Five classes of medication have shown higher efficacy than placebo for PD patients in randomized trials: SSRIs, SNRIs, high-potency benzodiazepines (BDZs), tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) (Bradwejn et al. 2005, Goddard et al. 2001, Mitte 2005, Otto et al. 2001, Susman and Klee 2005). With little differences among guidelines, SSRIs and the SNRI venlafaxine are currently considered as first line agents for PD patients because of their favourable ratio of benefits and side effects (American Psychiatric Association 2009, Bandelow et al. 2008, Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines team for panic disorder and agoraphobia 2003). Furthermore, pharmacotherapy is frequently delivered in association with psychotherapy (particularly cognitive-behavioural therapy (CBT)) because such association has been found to lead not only to the elimination of panic attacks and phobic symptoms, but also to a more persistent recovery (Bakker et al. 2005, Cloos 2005, Furukawa et al. 2007, Mattick et al. 1990).

To date, although a number of effective pharmacological treatments are available, current guidelines do not provide clear information about the relative benefit of each pharmacological compound over the others and about how an optimal treatment for each individual patient could be achieved. The aim of the present article is therefore to review available evidence focusing on comparative studies of antidepressants currently used for the treatment of PD and to evaluate possible differences among two or more drugs so as to define a more personalized approach for each individual patient. Higher emphasis will be given to drugs currently considered as first line treatment for PD. Afterwards, we will examine new therapeutic options that have recently been investigated to offer effective alternatives to patients who do not benefit from first line agents.

Selective serotonin reuptake inhibitors (SSRIs)

SSRIs (including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) are currently considered as a first-line treatment for PD. Such drugs mainly act through the inhibition of serotonin reuptake at the pre-synaptic serotonin pump thereby leading to increased levels of brain 5-HT (Vaswani et al. 2003). Many clinicians prefer SSRIs to other antidepressants because they are rarely lethal in overdose and have not serious effects on cardiovascular function. Nevertheless, SSRIs are associated with several side effects such as nausea and other gastrointestinal effects, headaches, irritability, insomnia, increased anxiety, drowsiness, tremor, sexual dysfunction and weight gain. Some of these adverse events (e.g., nausea) are usually transient, lasting no more than two weeks, while others (e.g., sexual dysfunction) commonly last for the whole duration of treatment.

As with TCAs, the initial low dose of the SSRI should be maintained for approximately 3–7 days, then gradually increased (e.g., in weekly increments) to a more standard daily dose, adjusting the timing of titration to the individual patient's tolerability, in order to limit the drop-out rate (Coplan et al. 1996). Indeed, if SSRIs are started at their therapeutic dose, patients may experience a neuro-vegetative syndrome characterized by agitation, insomnia and diarrhea. Furthermore, because SSRIs take time to lead to significant benefits and because they may initially increase anxiety symptoms, a temporary association with BDZs during the initial phase of antidepressant treatment can be considered (Goddard et al. 2001, Pollack et al. 2003).

Even though antidepressant's administration is not associated with physical dependence, patients should not abruptly discontinue these medications because of the risk of a withdrawal syndrome that is characterized by severe gastrointestinal and neurological symptoms (Zajecka et al. 1997). The syndrome begins a few days after discontinuation with dizziness, incoordination, headache, irritability, nausea, insomnia, and tends to resolve spontaneously within a couple of weeks. These kinds of symptoms are more likely to affect patients treated for several months with a short half-life antidepressant, and after a short period of tapering (Warner et al. 2006).

International guidelines suggest that 12 months should be the minimal duration of efficacious PD treatment, being SSRIs the treatment of choice. If the patient maintains a complete remission for 12 to 24 month, the physician can consider interrupting treatment that should be tapered slowly over a period of 2 to 6 months (Ballenger et al. 1998a, Bandelow et al. 2008). Note also that SSRI treatment of children and adolescents with PD should be considered with caution because there is evidence of increased risk of suicidal ideation and behaviour associated with these medications in young subjects (Marchesi 2008, Ravindran and Stein 2010).

Although all SSRIs proved efficacy for the treatment of PD, there are few data suggesting clear advantages of one SSRI over the others. A large number of such studies investigated the efficacy of paroxetine for PD patients. Indeed, paroxetine was the first SSRI that received the indication for the treatment of PD. Paroxetine seems to have the highest affinity for the human serotonin transporter as compared with other SSRIs (Owens et al. 2008, Owens and Nemeroff, 1994). It is also a modest inhibitor of the human NE transporter (Bang and Keating 2004) and its affinity for the muscarinic cholinergic receptor is greater than that of other SSRIs (Hyttel 1994, Thomas et al. 1987).

Several short-term studies found paroxetine superior to placebo in lowering anxiety levels and panic symptoms. For example, Ballenger et al. (Ballenger et al. 1998b) reported that patients taking paroxetine at the dose of 40 mg/day experienced significantly greater global improvement in frequency and intensity of panic attacks, intensity of anxiety, phobic fear, and depressive symptoms that frequently coexist with PD. Also, Oehberg et al. (Oehrberg et al. 1995) showed that response rates to paroxetine (20 to 60 mg/day), as measured with the Hamilton Anxiety Scale (HAMA) (Maier et al. 1988), were significantly higher than those observed in the placebo group. In another placebo

controlled study in which patients were treated with paroxetine (20 to 60 mg/day), clomipramine (50-150 mg/day) and placebo, paroxetine produced significant improvements compared with placebo on various measures of panic attacks frequency and it was as effective as clomipramine, though it was associated with less adverse events (Lecrubier et al. 1997).

Most importantly, paroxetine has also been compared with other antidepressants. In a double blind randomized controlled trial paroxetine was therapeutically equivalent to sertraline for the treatment of PD patients, but there were notable difference in the tolerability of both acute treatment and gradual taper from medication. Indeed, more patients taking paroxetine discontinued the trial due to side effects and the medication taper resulted in a significantly greater clinical worsening among patients treated with paroxetine as compared with those treated with sertraline (Bandelow et al. 2004). A possible explanation of such findings could be related to the notion that paroxetine is the most powerful inhibitor of 5-HT and NE uptake among SSRIs (Thomas et al. 1987) and the discontinuation of such drug could therefore be related to a higher likelihood of withdrawal symptoms. Moreover, Perna et al. (Perna et al. 2001) found that paroxetine seemed effective for the treatment of PD at lower doses than citalopram (30 mg vs. 40 mg, respectively), although both drugs were equally tolerated. Such finding could be explained by the notion that paroxetine has a more potent effect upon the serotonergic system as compared with citalopram (Hyttel, 1994) and has a higher sedative profile that could be associated with significant benefits on anxiety symptoms, even at lower dosages.

Furthermore, two placebo controlled short-term trials have been carried out that studied the efficacy and tolerability of paroxetine and venlafaxine in treating PD patients: in the former study (Pollack et al. 2007a), patients who received venlafaxine (75 mg/day or 150 mg/day) or paroxetine (40 mg/day) experienced significantly greater improvement on most efficacy outcome measures as compared with those who received placebo. The authors did not find significant differences between the two venlafaxine-treated groups and between the venlafaxine- and paroxetine-treated groups. In the latter study (Pollack et al. 2007b), each of the three active treatment groups (venlafaxine 75 mg/day and 225 mg/day, paroxetine 40 mg/day) had a significantly higher proportion of patients who were free of full-symptom panic attacks than the placebo group. However, venlafaxine 225 mg/day was more efficacious than paroxetine on the reduction of Panic Disorder Severity Scale (PDSS) (Shear et al. 1997) scores and of the total number of panic attacks at endpoint. This finding suggests that the combined effects of serotonin and NE might provide patients with a significant advantage over serotonin alone and highlights the possibility of a dose-response relationship for venlafaxine in the pharmacological treatment of PD. Of note, in both studies all active treatments were overall well tolerated.

In a single-blind controlled trial (Bertani et al. 2004), paroxetine was significantly more efficacious than a pure noradrenergic drug, reboxetine, in reducing the Panic Associated Symptoms Scale (Argyle et al. 1991) (PASS) score, confirming that the serotonin dysfunction could play a more important role in the pathophysiology of PD than noradrenaline. It is noteworthy, however, that the small sample included in this study could reduce the significance of these findings. Finally, Montanés-Rada et al. (Montanes-Rada et al. 2005) did not observe any significant differences in terms of efficacy on panic symptoms between paroxetine and mirtazapine. However, the results of such study were limited by the lack of randomization and the use of a single blind design.

In conclusion, there are currently no consistent data that reveal a clear advantage of paroxetine over other SSRIs and mirtazapine, even though paroxetine seems more effective than reboxetine. On the other hand, a significant difference favouring venlafaxine was observed in a study comparing paroxetine with venlafaxine 225 mg, although only on a limited number of measures. However, because of the small number of studies comparing these antidepressants and because of the lack of appropriate designs we cannot draw definitive conclusions. Accordingly, we suggest that the appropriate choice between paroxetine and other antidepressants should take into account the specific tolerability profile of such drug and the specific need of each patient.

Sertraline is another widely used SSRI that has been investigated in several studies for the treatment of PD patients. It is 2-10 times more potent in inhibiting serotonin reuptake than fluvoxamine and fluoxetine (Koe 1990) and it is 60 times more potent in inhibiting 5-HT than either NE or dopamine (Bolden-Watson and Richelson 1993). In a short-term multicentre trial (Pohl et al. 1998), the reduction in panic attacks frequency at endpoint was significantly greater in the sertraline group than in the placebo group and a higher proportion of sertraline-treated patients than placebo-treated patients were free of panic attacks at endpoint. The therapeutic response of sertraline (50 to 200 mg/day) occurred rapidly and such antidepressant was also well tolerated. In a different study, Pollack et al. (Pollack et al. 1998) showed that at the end of their short-term trial, patients receiving sertraline exhibited significantly greater reductions in the number of panic attacks and in the global severity of illness than did patients treated with placebo. Moreover, relatively few subjects discontinued sertraline because of adverse events. In addition, Londborg et al. found that sertraline (50 mg/day) was superior to placebo not only in reducing the frequency of panic attacks, but also in reducing anticipatory anxiety, time spent worrying and limited symptoms' panic attacks.

Other studies evaluated the effectiveness and tolerability of sertraline in comparison with imipramine. Sertraline and imipramine were found to have significant and equivalent efficacy in the treatment of PD. The most notable difference between such antidepressants was the higher tolerability of sertraline, being such drug associated with lower side effects burden and with a significantly lower discontinuation rate due to adverse events than imipramine (Lepola et al. 2003, Mavissakalian 2003). Among SSRIs, sertraline was contrasted with paroxetine in a single randomized controlled double blind short-term study. As discussed in more detail above, the authors reported that both

SSRIs showed equivalent efficacy for PD (Bandelow et al. 2004). However, in such study, sertraline showed a higher tolerability profile and it was associated with lower discontinuation rates due to side effect and less weight gain as compared with paroxetine. Moreover, contrary to paroxetine, sertraline taper was associated with sustained improvement in panic symptoms. Overall, the results of this study confirmed previous findings in other psychiatric disorders that showed that sertraline was associated with fever adverse events and withdrawal symptoms as compared with paroxetine (Fava et al. 2000, Hindmarch et al. 2000, Michelson et al. 2000, Rosenbaum et al. 1998). In conclusion, sertraline could be a good and well-tolerated option for PD treatment. However, there is not enough evidence to unequivocally state that sertraline is more or less effective than other antidepressants for the relief of panic symptoms and anxiety levels so far.

Fluoxetine and fluvoxamine were found to be efficacious for the reduction of panic symptoms as well. Pertaining to fluoxetine, such drug is less selective for the serotonin reuptake. It has a longer elimination half-life and is less likely to be associated with this discontinuation syndrome as compared with other SSRIs (Lamb 2000). Several studies have suggested that fluoxetine could be an efficacious and safe drug for PD patients. As an example, Michelson et al. (Michelson et al. 1998) found that fluoxetine, particularly the 20-mg/day dose, was associated with a significantly higher improvement than placebo across multiple symptom measures, including total panic attacks frequency, phobic symptoms and overall anxiety. In a following short-term study (Michelson et al. 2001), the same authors revealed that this antidepressant was associated with a significantly greater proportion of panic-free patients compared with placebo after 6 weeks of treatment with 20 mg daily and after 12 weeks at doses up to 60 mg daily. Discontinuations due to adverse events among fluoxetine- and placebo-treated patients were similar and low.

Amore et al. in a double blind randomized flexible dose study contrasted fluoxetine with imipramine in the acute and long-term treatment of PD (Amore et al. 1999a). Fluoxetine had a quicker effect than imipramine in reducing anxiety levels as measured with the HAMA at the end of the first week of treatment. However, no significant differences were found in the effectiveness of fluoxetine and imipramine on the total number of panic attacks, anticipatory anxiety and phobia severity. On the other hand, fluoxetine was better tolerated than imipramine. Moreover, the same authors compared fluoxetine with citalopram in a short- and long-term study (Amore et al. 1999b). In such study, HAMA mean scores indicated that fluoxetine was more effective than citalopram on the reduction of anxiety levels at the end of the first and the second week of treatment. Full remission of panic symptoms was first reached at the end of the 4th week in the fluoxetine group and at the end of the 6th week in the citalopram group. These results suggest that probably fluoxetine could provide benefits on panic symptoms and anxiety levels earlier than citalopram. Finally, fluoxetine was contrasted with mirtazapine in a randomized double-blind flexible-dose trial (Ribeiro et al. 2001). This study did not show any

differences between treatments in terms of efficacy, aside from patient global evaluation of phobic anxiety that favoured mirtazapine. Discontinuation rates did not differ between groups. Both drugs were overall well tolerated being nausea and headache most common among fluoxetine-treated patients and drowsiness and weight gain most common among mirtazapine-treated patients. Overall, these data suggest that mirtazapine may be an alternative choice for PD patients, leading to improvements similar to those obtained with fluoxetine in many clinical dimensions of panic.

Fluvoxamine was investigated in many studies focusing on PD patients as well. Fluvoxamine is a SSRI that, in addition to the inhibition of the reuptake of serotonin, has a little effect on dopamine and NE uptake systems. It also binds to sigma1 receptors and has a low affinity for neurotransmitter receptors (Leonard 1992, Narita et al. 1996). Several trials found that fluvoxamine was superior to placebo for the treatment of panic symptoms. Black et al. (Black et al. 1993) revealed that patients receiving fluvoxamine showed a greater reduction in their mean panic attack severity score than those receiving placebo after 4 weeks and after 8 weeks at the end of the study. Drop-out rate because of adverse effects was common in the group treated with fluvoxamine, however a significantly higher dropout rate for inefficacy was observed in the placebo group. Furthermore, a further short-term study showed that, by the end of the treatment period, a significantly higher proportion of patients treated with fluvoxamine were free from major and minor panic attacks than patients taking placebo (Hoehn-Saric et al. 1993). Similar results were found in other double-blind randomized controlled studies (Asnis et al. 2001, Den Boer and Westenberg 1990, Hoehn-Saric et al. 1994).

Fluvoxamine was also contrasted with maprotiline (Den Boer and Westenberg 1988), a specific NE reuptake inhibitor with only weak effects on 5-HT and dopamine reuptake (Muller 2008). Findings from this double blind trial indicated that fluvoxamine (150 mg/day) significantly reduced the number of panic attacks and the depressive symptomatology associated with anxiety symptoms. On the other hand, maprotiline (150 mg/day) had no effect on anxiety levels and the number of panic attacks did not significantly change from baseline to endpoint. Maprotiline had only a slight effect on the depressive symptoms as well. These results support the hypothesis that a dysfunction of the serotonergic pathways in the brain plays a central role in the pathogenesis of PD. In a different double blind short-term study (Den Boer and Westenberg 1990), PD patients were treated with fluvoxamine (150 mg/day), ritanserin (20 mg/day), a specific 5-HT2 receptor antagonist, or placebo. Treatment with fluvoxamine resulted in a significant reduction in the number of panic attacks and avoidance behaviour, whereas treatment with ritanserin appeared to be ineffective. Of note, while these data support an important role of 5-HT in the pathophysiology of PD, they do not support the existence of a supersensitivity of 5-HT2 receptors in PD subjects. On the other hand, no short-term controlled studies comparing fluvoxamine with other SSRIs for PD treatment have been carried out thus far.

Summarizing data from literature, we conclude that fluvoxamine is a potent anti-panic agent with a rapid

onset of action (Den Boer and Westenberg 1988, Den Boer and Westenberg 1990) that it is generally well tolerated (Riddle et al. 2001, Wagner et al. 1996). As with other SSRIs, the most commonly reported adverse events are gastrointestinal, particularly nausea. Of note, fluvoxamine is associated with a lower risk of sexual dysfunction and withdrawal syndrome than other SSRIs (Figgitt and McClellan 2000).

Finally, citalopram showed efficacy for the reduction of panic symptoms as well. Citalopram has the highest selectivity for inhibiting the 5-HT reuptake among SSRIs (Baumann 1996). It also shows some affinity to α-1-adreno-receptors and it slightly blocks histamine H1 receptor (Owens et al. 1997). In an early short-term randomized controlled trial (Wade et al. 1997), citalopram was compared to placebo and clomipramine. Citalopram (20-60 mg/day) was significantly more effective than placebo in reducing the number of panic attacks and anxiety levels and as effective as clomipramine (60-90 mg/day) on the HAMA score. Note that the percentage of responders at week 8, measured by the CAS panic attack item, was higher in the group of patients taking citalopram 20-30 mg than those taking clomipramine. These data suggest that the 20-30 mg dose tended to provide a better response than the higher citalopram dose and than clomipramine. A following study by Lepola et al. (Lepola et al. 1998) confirmed these findings as well. Moreover, citalopram was significantly more efficacious than placebo not only in decreasing the frequency of panic attacks, but also in alleviating phobic symptoms and avoidance behaviour (Leinonen et al. 2000). In a different double blind placebo randomized controlled study (Stahl et al. 2003), citalopram (20-40 mg/day) was compared with its therapeutically active S-enantiomer escitalopram (10-20 mg/day). In such study both antidepressants significantly reduced PD symptoms and severity as compared with placebo at endpoint (10 weeks). However, the proportion of patients with zero panic attacks at study endpoint was 50% for the escitalopram group and 38% for either citalopram and placebo groups suggesting that escitalopram could provide PD patients with a higher advantage than citalopram.

Rampello et al. (Rampello et al. 2006) also compared the efficacy and safety of citalopram (20 mg/day) with those of escitalopram (10 mg/day) in elderly patient suffering from panic attacks. Both drugs showed the same efficacy in lowering the scores of HAMA. However, in patients taking escitalopram, the authors observed a significant reduction of panic attack rates and an improvement of the anxious and depressive symptoms as soon as two weeks following the initiation of treatment. This finding suggests that escitalopram could have a more rapid onset of action and could provide patients with the same benefits of citalopram at lower dosages. Indeed, in vivo studies have found that escitalopram is twice as potent as citalopram in inhibiting serotonin reuptake and it is four times more potent than citalopram in reducing fire activity of serotonergic neurons as well (El Mansari et al. 2005, Owens et al. 2001). Of note, in such study the dropout rates were relatively low and nearly equally distributed between subjects treated with citalopram and those treated with escitalopram. In conclusion, citalopram and

escitalopram treatment could result in a significant improvement of PD symptoms without causing important adverse events. In particular, the favourable low side effects profile of escitalopram is of considerable relevance due to the chronic nature of this psychiatric illness.

SSRIs proved efficacy in the long-term treatment of PD as well (Dannon et al. 2007). Many studies report that this class of antidepressants are superior to placebo in the maintenance therapy of PD (Lecrubier and Judge 1997, Lepola et al. 1998, Michelson et al. 1999, Sharp et al. 1996). According to current guidelines, twelve months should be the minimal duration of an efficacious treatment for PD patients (American Psychiatric Association 2009). As previously argued, maintenance therapy with SSRIs is important because of the lower propensity of relapses to occur following a long-term treatment (Dannon et al. 2007, Lecrubier and Judge 1997). However, many patients discontinue maintenance treatment with SSRIs because of the onset of weight increase, sexual side effects, irritability, affective bluntness, and cognitive alterations, such as memory and concentration disturbances (Dannon et al. 2007, Kinzl 2009, Toni et al. 2004, Toni et al. 2000). Moreover long-term therapy is associated, in some cases, with hyperprolactinaemia and extrapyramidal parkinsonian-like effects (McKenzie and Risch 1995)

In spite of the importance of information as to the long-term treatment of PD, little evidence is available about the long-term efficacy and tolerability of antidepressants for the treatment of PD. Dannon et al. in one of the first naturalistic studies that examined the effectiveness of paroxetine therapy (up to 24 months) for relapse prevention, found that paroxetine was highly efficacious both in the short-term and in the long-term treatment of PD (Dannon et al. 2004). The authors also reported that paroxetine was overall well tolerated, being increased appetite, weight gain and sexual dysfunction most common side effects.

Furthermore Lecrubier and Judge studied the long-term effects of paroxetine (20-60 mg/day) in comparison with clomipramine (50-150 mg/day) and placebo (Lecrubier and Judge 1997). They found that the efficacy of paroxetine in reducing panic symptoms was maintained into the long-term period as well. Paroxetine was not only superior to placebo, but also as efficacious as clomipramine in reducing the number of full panic attacks relative to baseline. Further improvements were observed with continued therapy, suggesting the need for long-term treatment of PD. Findings from this study also indicated that paroxetine was better tolerated than clomipramine. Indeed, withdrawal due to adverse effects occurred more frequently in the clomipramine group (19%) than in the paroxetine group (7.4%). Paroxetine was also compared with TCAs in a 3-year naturalistic prospective study (Toni et al. 2000). The authors found that, although a progressive improvement was recorded in more than 70% of the cases from the first month of treatment onwards, remission rates progressively increased over a period ranging from 5 to 8 months. The global tolerability of paroxetine, clomipramine and imipramine appeared excellent. At the end of the study, weight gain appeared to be the most relevant side effect associated with both TCAs and paroxetine, whereas

anticholinergic side effects were more common with TCAs.

Moreover, Marchesi et al. in a 1-year naturalistic study, found that paroxetine and citalopram did not differ in reducing the number of panic attacks and the intensity of anticipatory and phobic anxiety at endpoint (Marchesi et al. 2005, Marchesi et al. 2006b, Marchesi et al. 2006c). Indeed, the full remission of symptoms was similar in patients treated with paroxetine (33.5±13.3 mg/day) or with citalopram (34.7±15.2 mg/day). In a following 3 years naturalistic study (Nardi et al. 2012), paroxetine (38.4±3.74 mg/day) was contrasted with clonazepam (1.9±0.30 mg/day) in PD treatment. At endpoint, the authors observed significant and equal decreases in the number of panic attacks per month for both treatments and no significant differences in the severity of anxiety. Concerning adverse events during long-term treatment, a significantly higher proportion of patients in the paroxetine group than in the clonazepam group experienced sexual dysfunction, drowsiness/fatigue, diarrhea/constipation, dry mouth, excessive sweating, tremor and nausea. On the other hand, subjects taking clonazepam mainly complained of drowsiness, fatigue and memory/concentration problems.

In a different randomized double blind long-term study, sertraline was compared with imipramine (Lepola et al. 2003). Both antidepressants had significant and equivalent efficacy in treating PD patients in the long-term treatment. However, sertraline was associated with lower drop-out rates than clomipramine. Two side effects were significantly more frequent in subjects taking sertraline than in those taking imipramine: nausea and diarrhea. In contrast, dry mouth, dizziness, sweating, constipation and tremor appeared more frequently in the clomipramine group.

Michelson et al. (Michelson et al. 1998), employing a randomized controlled design, studied the efficacy of fluoxetine in the short and long-term PD treatment. Patients who completed 10 weeks of acute treatment and attained a clinician-rated Clinical Global Impressions (CGI) (Guy 1976) improvement score of 1 or 2 could enter in a 24-week continuation phase with random assignment to continued therapy with their acute-phase dose or placebo. Data at the end of the trial showed that fluoxetine-associated improvement appeared to have continued during the extension phase, and relapse rates were numerically lower in patients who continued fluoxetine treatment. Overall, fluoxetine was considered well tolerated.

Also, fluoxetine was compared with imipramine in a long-term randomized double blind trial (Amore et al. 1999a). No significant differences were found between the antidepressants in term of efficacy. High rates of persistent remission were observed with both drugs. Moreover, fluoxetine was safer and better tolerated than imipramine. Indeed, in the fluoxetine group side effects were scarcely relevant, while in the imipramine group anticholinergic effects led to greater distress. The same authors contrasted fluoxetine (20±10 mg/day) with citalopram (40±10 mg/day) in a 1-year double blind randomized trial (Amore et al. 1999b). Long-term evaluation demonstrated high rates of persistent full remission with both fluoxetine and citalopram. No differences were recorded in the

evaluation of frequency and severity of adverse effects in both groups. Furthermore, Tiller et al. in a multicentre double blind long-term trial, found fluoxetine and moclobemide efficacious and tolerated treatment options for acute panic treatment as well as for maintenance therapy. Indeed, at 1 year, 97 % of patients treated with moclobemide (n = 61) and 100% of patients treated with fluoxetine (n = 65) remained much improved (Tiller et al. 1999).

In addition, in a randomized double blind 1-year trial (Lepola et al. 1998), patients were assigned to 1 or 3 fixed dosage ranges of citalopram (10 or 15 mg/day, 20 or 30 mg/day, or 40 or 60 mg/day), 1 dosage range of clomipramine (60 or 90 mg/day), or placebo. Cumulative response rates, as measured with the Clinical Anxiety Scale (CAS) (Snaith et al. 1982) panic attack item, showed further increases and continued to be significantly higher in all active groups compared with placebo during the long-term treatment. The pattern of adverse events was similar to that observed in the short-term phase. Tremor and dry mouth were significantly more frequent in subjects treated with clomipramine than in those treated with citalopram.

Finally, Dannon et al. (Dannon et al. 2006), in a long-term open label randomized trial, compared citalopram, fluoxetine, fluvoxamine and paroxetine in order to study their efficacy and tolerability in PD patients. Most patients who completed the 12-month study protocol had a favourable response to the treatments under investigation. At the end of the trial, the clinical improvement observed in the 4 groups was similar and there were no significant differences in treatment response and relapse rates. In the initial phase of treatment, side effects, including gastrointestinal symptoms, agitation, palpitations and insomnia, were similar among all 4 SSRIs. However, the intensity and the frequency of adverse events were greatest among patients treated with fluvoxamine. Moreover, at the 12th month end point patients in all 4 treatment groups had a significant increase in body weight, although the weight gain in patients taking fluvoxamine was significantly lower compared with that observed in patients treated with the remaining 3 SSRIs. Complaints about sexual dysfunctions were frequent and similar in citalopram, fluoxetine and paroxetine group, while subjects treated with fluvoxamine reported a lower incidence of this type of side effect.

In conclusion, SSRIs are all associated with a good treatment response. Indeed, they provide great benefits on panic symptoms and anxiety levels improving PD patients' quality of life. SSRIs proved efficacy both in short- and long-term treatment of PD leading to an improvement of panic symptoms and to a good prevention of panic relapses. There is evidence that they are as efficacious as TCAs in treating PD patients but associated with a better tolerability profile and with lower drop-out rates. Moreover, some data suggest that SSRIs have a more rapid onset of action than TCAs (Lecrubier and Judge 1997).

Differences among SSRIs mainly concern the side effects profile and the onset of action. As an example we have found that paroxetine is associated with higher drop-out rates due to side effects, in particular weight gain, and with more sever withdrawal symptoms than sertraline. Moreover, paroxetine seems effective for PD

treatment at lower dosages than citalopram. Fluoxetine seems to have a quicker onset of action as compared to citalopram. On the other hand, fluvoxamine could be associated with more intense and frequent adverse events in the acute treatment but with less weight gain and sexual side effects in the maintenance phase than other SSRIs. Finally, escitalopram could have a more rapid onset of action and a better tolerability profile than citalopram. It also could provide patients with the same benefits of citalopram at lower dosages. Concerning the comparison between SSRIs and other antidepressants we found that paroxetine 40 mg/day could be less efficacious than venlafaxine 225 mg/day in reducing the number of panic attacks to zero. Furthermore, paroxetine seems to be superior to reboxetine and as effective as mirtazapine in treating PD patients.

In sum, although many studies have investigated the efficacy and tolerability of SSRIs in the treatment of PD, there are not consistent data suggesting advantages of one of such antidepressants over the others. Moreover, data are lacking as to which pharmacological compound can be best tailored to the specific needs of each individual patient. Future studies about the pharmacological treatment of PD should not only more deeply investigate the differences among the antidepressants in terms of effectiveness, side effect profile and onset of action, but they should also evaluate the influence of possible moderators of outcome such as gender, age, comorbidities and duration of illness. This kind of information could be valuable for clinicians and would help them treat each subject more adequately.

Serotonin and norepinephrine reuptake inhibitors (SNRIs)

SNRIs, including venlafaxine, duloxetine and milnacipran, have shown efficacy for the treatment of several anxiety disorders including PD (Dell'Osso et al. 2010, Silverstone 2004, Stahl et al. 2005). This is not surprising because consistent evidence supports the hypothesis that NE, in addition to 5-HT, could be involved in the pathophysiology of anxiety (Ressler and Nemeroff 2000). SNRIs inhibit both the reuptake of NE and that of 5-HT increasing the availability of such neurotransmitters in the central nervous system. They have also little affinity for muscarinic, cholinergic, H1-histaminic and α-adrenergic receptors (Kent 2000).

This class of antidepressants is generally efficacious in alleviating panic symptoms and anxiety levels and it is relatively safe in overdose (Pollack et al. 2007b, Pollack et al. 2007c). However, similarly to SSRIs, SNRIs could be associated with several adverse events such as nausea, headache, dizziness, somnolence and sexual dysfunction (Silverstone 2004). Nonetheless, there is evidence that asthenia, fatigue, somnolence and nausea are less frequent in subjects treated with SNRIs as compared with those treated with SSRIs (Freire et al. 2011) and SNRI are overall less likely than other drugs to have negative effects on body weight (Freire et al. 2011). Moreover, sweeting, palpitations, dry mouth and constipation, probably related to the noradrenergic stimulation, are often associated with SNRIs treatments (Stahl et al. 2005). Finally, SNRIs, as well as SSRIs, can be associated with discontinuation symptoms and take some weeks to provide significant benefits (Silverstone 2004).

Among SNRIs, venlafaxine is certainly the antidepressant that has been most extensively studied. Such drug inhibits both the 5-HT and the NE reuptake, though it has a higher affinity for the 5-HT transporter than for the NE transporter (Muth et al. 1986). The NE reuptake inhibition increases exponentially at doses above 150 mg (Morilak and Frazer 2004). Moreover, venlafaxine has a little affinity for the dopamine transporter (Muth et al. 1986). Indeed, this weak interaction with dopamine receptors may have clinical applicability only at very high doses. Finally, venlafaxine does not seem to bind to muscarinic, cholinergic and α1-adrenergic receptors in vitro, which are thought to be associated with anticholinergic, sedative and cardiovascular effects, sometimes observed with other antidepressants (Feighner 1999).

The first placebo controlled studies investigating the efficacy and tolerability of venlafaxine in PD patients reported that patients treated with venlafaxine experienced significant greater global improvement than those taking placebo. Venlafaxine was also well tolerated when administered with a gradual upward dose titration (Pollack et al. 1996). In two following double blind randomized controlled short-term studies, Pollack et al. compared venlafaxine (75 mg/day, 150 mg/day and 225 mg/day) with both placebo and paroxetine (40 mg/day) (Pollack et al. 2007b, Pollack et al. 2007a). Both active treatments were more effective than placebo and overall well tolerated being sweating, dry mouth and anorexia the most common adverse effects among patients treated with venlafaxine. On the other hand, subjects taking paroxetine complained more often of somnolence, sweating and constipation.

No significant differences were observed between active treatment groups in terms of effectiveness. However, as previously reported, the group treated with venlafaxine 225 mg/day showed a significantly higher improvement than the group treated with paroxetine on PDSS score. A possible explanation for the higher efficacy of venlafaxine at higher dosages could be imputed to the notion that at such dosage its effects on the serotonergic system are accompanied by concurrent effects on the adrenergic system and the combination of such two effects could lead to the increased efficacy observed in clinical trials (Feighner 1999). In conclusion, venlafaxine is considered as a first-line agent for PD treatment because it is effective in relieving patients' symptoms, it is generally safe and prevents relapses in PD outpatients (Ferguson et al. 2007). However, it is noteworthy that venlafaxine should not be prescribed to patients with cardiac abnormalities because the stimulating of the NE transmission can increase blood pressure (Feighner 1995).

Pertaining to duloxetine and milnacipran, no placebo controlled trials in PD patients have been performed so far. Both SNRIs are virtually equipotent in inhibiting the 5-HT and NE reuptake (Preskorn 2004, Wong and Bymaster 2002, Wong et al. 1993). Currently, their main indication is for subjects suffering from major depression. Available data (Blaya et al. 2007, Cia et al. 2006, Lai and Hsu 2011, Lai and Wu 2011, Simon et

al. 2009) provide preliminary support for the efficacy of duloxetine and milnacipran for the treatment of PD patients. Of note, both drugs are associated with a favourable side effects profile, in particular with lower rates of sexual dysfunction in comparison with venlafaxine and SSRIs (Clayton et al. 2007, Deakin and Dursun 2002, Delgado et al. 2005, Serretti and Chiesa 2009, Werneke et al. 2006). Finally, contrary to venlafaxine, duloxetine and milnacipran do not significantly increase blood pressure (Guelfi et al. 1998, Montgomery et al. 1996, Schatzberg 2003). Overall, current evidence suggests that properly powered randomized placebo controlled studies comparing such drugs to placebo as well as to other active compounds are warranted.

Other antidepressants

In addition to the antidepressants mentioned above, other antidepressants have been put forth as candidate treatment options for the treatment of PD patients, even though they have been less extensively studied. Such antidepressants include, among others, mirtazapine, reboxetine and bupropion.

Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA) that amplifies noradrenergic transmission via blockade of α2-adrenoceptors (de Boer 1995, de Boer 1996) and enhances serotonergic transmission indirectly, via noradrenergic stimulation of α1-adrenoceptors and blockade of α2-heteroreceptors (De Montigny et al. 1995). Although its main indication concerns the treatment of MD (Fawcett and Barkin 1998), this drug has shown efficacy for several anxiety disorders as well (San and Arranz 2006).

To date, no double blind placebo-controlled studies focusing on the use of mirtazapine in the treatment of PD have been performed. However, several open-label trials (Carli et al. 2002, Carpenter et al. 1999, Ilies-Alexandru and Zaharia 2002, Sarchiapone et al. 2003) found that mirtazapine could be efficacious for such patients even when it was compared with some SSRIs (Montanes-Rada et al. 2005, Ribeiro et al. 2001). In particular, Montanés-Rada et al. observed that, after 3 weeks of treatment, subjects treated with mirtazapine (30 mg/day) showed significantly higher clinical improvements than those treated with paroxetine (20-30 mg/day) (Montanes-Rada et al. 2005), although no significant difference at endpoint could be observed. This result suggests that mirtazapine could be associated with a faster response as compared with paroxetine. Moreover, mirtazapine was associated with a lower percentage of dropouts due to adverse events than paroxetine. The most common side effects reported in the mirtazapine group were weight gain and drowsiness, while the paroxetine group showed a higher complain of headache, sexual dysfunction and gastrointestinal side effects. Note, however, that the sedative profile of mirtazapine could have influenced the observed results and further analyses aimed at exploring perceived quality of life of patients treated with mirtazapine as compared with those treated with other antidepressants such SSRIs are needed.

The most frequent side effects associated with mirtazapine treatment are drowsiness, increased appetite, weight gain, somnolence, blurred vision, muscle pain, tiredness, headache and apathy (Carli et al. 2002, Montanes-Rada et al. 2005, Ribeiro et al. 2001). However, data from literature also suggest that mirtazapine is associated with a good tolerability profile (Benjamin and Doraiswamy 2011). In addition, contrarily to other antidepressants, no significant difference between mirtazapine and placebo was observed in terms of sexual dysfunction (Serretti and Chiesa 2009). Also, mirtazapine's side effect profile might make it a better agent for specific patient populations. For example, patients with high anxiety levels, patients who are unable to tolerate the initial tremors associated with SSRIs, patients complaining sexual dysfunction as well as patients suffering from significant insomnia might benefit from mirtazapine treatment (Benjamin and Doraiswamy 2011).

Reboxetine is a selective noradrenaline reuptake inhibitor that has no significant effects on histaminic or cholinergic receptors or on adrenergic receptors (Brunello and Racagni, 1998) and showed significant efficacy for MD (Schatzberg 2000). Although data from literature suggest that this pharmacological agent could be efficacious for PD patients (Dannon et al. 2002, Seedat et al. 2003, Versiani et al. 2002), to date only one study has been published that investigated the efficacy of reboxetine in comparison with placebo for PD treatment (Versiani et al. 2002). The results of such trial suggested that reboxetine was significantly more effective than placebo in reducing the final mean number of panic attacks and phobic symptoms. However, an important limitation of this study was the concomitant use of anxiolytic drugs that did not allow to understand to what extent reboxetine alone was efficacious in PD treatment. Moreover, it is worth mentioning that Bertani et al. in a single-blind randomized trial, comparing the effectiveness and tolerability of reboxetine and paroxetine, found that reboxetine was significant less effective than paroxetine on panic attacks. Indeed the reduction of PASS scores was significantly greater in the paroxetine group than in the reboxetine one. On the other hand, the results of such study showed a significant greater frequency of weight gain and sexual dysfunction in the paroxetine group whereas the only side effect that was more likely to occur in patients treated with reboxetine was dry mouth.

Reboxetine is generally well tolerated: indeed, less than 5% of patients treated with reboxetine drop out for side effects (Dannon et al. 2002, Seedat et al. 2003, Versiani et al. 2002). Other adverse effects related to reboxetine treatment included nausea, tachycardia, constipation, drowsiness, decreased appetite, blurred vision, sweating and insomnia (Bertani et al. 2004, Seedat et al. 2003, Versiani et al. 2002). To date, data from literature about reboxetine in PD patients are not consistent to draw definitive conclusions. Randomized controlled studies of sufficient simple size are needed to extend these preliminary results and to confirm both efficacy and tolerability. Note, however, that because the serotonergic dysfunction is thought to play a more significant role into the aetiology of PD as compared with the noradrenergic dysfunction (Maron and Shlik 2006), reboxetine might not be as effective for the

treatment of PD patients as drugs acting upon the serotonergic system.

Bupropion is an atypical antidepressant that belongs to the class of aminoketones. It is a non-tricyclic antidepressant that differs from commonly prescribed antidepressants, as its primary pharmacological action involves the norepinephrine-dopamine reuptake inhibition. It binds selectively to the dopamine transporters, even though its clinical effects are probably mainly due to its inhibition of the norepinephrine reuptake (Learned-Coughlin et al. 2003, Terry and Katz 1997). Bupropion also acts as a nicotinic acetylcholine receptors antagonist (Fryer and Lukas 1999, Slemmer et al. 2000) and it has not anticholinergic, antihistaminergic and antiserotonergic properties (Ferris and Beaman 1983, Ferris et al. 1982). Pertaining to PD treatment, placebo controlled studies investigating the usefulness of bupropion are lacking thus far. To date, only two small open studies have been performed with contrasting results (Sheehan et al. 1983, Simon et al. 2003), suggesting that it is unlikely that this drug could have significant effects on PD symptoms.

Tricyclic antidepressant (TCAs) and monoamine oxidase inhibitors (MAOIs)

TCAs have been used in psychiatry since the late 1950s. They work by inhibiting both 5-HT and NE reuptake from the synaptic cleft (Feighner 1999). The two TCAs that have been most extensively studied for the treatment of PD are clomipramine and imipramine. Evidence from several randomized-controlled trials indicates that both drugs are more effective than placebo in the acute treatment of PD (Fahy et al. 1992, Mavissakalian and Perel 1989, Mavissakalian and Perel 1995, McTavish and Benfield 1990, Modigh et al. 1992, Sheehan et al. 1988, Taylor et al. 1990) with regard to the reduction of the number of panic attacks, the decrease of anticipatory anxiety and, in some case, the reduction for the need of concurrent benzodiazepine use (Andersch et al. 1991). There is also consistent support for the use of imipramine and clomipramine as a maintenance treatment for PD patients (Lecrubier et al. 1997, Mavissakalian and Perel 1999).

The main limiting factor to more widespread use of TCAs is their side effect profile, which includes anticholinergic and antiadrenergic effects such as sedation, constipation, dry mouth, orthostatic hypotension, and sexual dysfunction (McTavish and Benfield 1990, Monteiro et al. 1987) as well as their well-documented risk of cardiovascular toxicity in overdose (Power et al. 1995). These factors, along with the comorbid depression and elevated risk of suicide in PD, have largely relegated TCAs to third- or fourth-line agents in refractory PD.

MAOIs are an old class of antidepressant that may be useful as third-, fourth-line treatment when both SSRIs and TCAs have not yielded acceptable results in PD patients. They acts by irreversibly inhibiting the enzyme monoamine oxidase, which is responsible for the breakdown of monoamines, 5-HT, NE and dopamine, resulting in a net increase in the availability of these neurotransmitters in the synaptic cleft. Among them, phenelzine is the most studied antidepressant in association with PD and its efficacy is well established on the basis of placebo-controlled studies (Ballenger, 1993) and when compared with imipramine and alprazolam (Sheehan et al. 1980, Tesar and Rosenbaum, 1993). MAOIs share several side effects associated with TCAs, they can produce severe hypertensive crises when ingested with tyramine (Stahl and Felker 2008) and they can determine dangerous drug-drug interactions (Boyer and Shannon 2005, Gillman 2005). More recently, a reversible monoamine oxidase inhibitor (RIMA), moclobemide, has been investigated for the treatment of PD, with contrasting reports (Kruger and Dahl 1999, Tiller et al. 1999, Uhlenhuth et al. 2002). The main advantage of this drug in comparison with older MAOIs is that patient is not subject to dietary restriction.

Predictors of response to pharmacotherapy in Panic Disorder

Although progress has been made in the development of effective pharmacological and psychotherapeutic interventions, not all patients respond to treatment (Katon 2006). Such difficulty could be avoided if it were possible to predict *a priori* the response for each subject, matching each patient with his/her best predicted treatment option at early stages of treatment, thereby leading to significant enhancements of clinical outcomes.

Predictors of response include genetic, clinical, demographic and psychosocial factors as well as their reciprocal interactions. While there is converging support for a considerable genetic influence on the individual antidepressant treatment response (Malhotra et al. 2004, Serretti et al. 2005, Serretti et al. 2007a, Serretti et al. 2007b, Serretti et al. 2007c), only a few studies have specifically investigated the pharma-cogenetic underpinnings of anxiety disorders to date. Concerning PD, the COMT valine/methionine variant was associated with poor treatment response to paroxetine (Woo et al. 2004, Woo et al. 2002) while the serotonin transporter promoter region long variant (5HTTLPR) could be associated with a better response to paroxetine, although this could be true only in females (Perna et al. 2005). Moreover, a recent study reported that the 5-HT1A receptor-1019 C/G polymorphism could be strongly predict a better response to SSRIs (Yevtushenko et al. 2010).

Among clinical factors, an axis I comorbidity seems to be a negative predictor of response in the majority of the long-term studies (Kipper et al. 2007, Slaap and den Boer 2001). On the other hand, an axis II comorbidity and a more severe illness seem to be strong predictors of non-response to TCAs, SSRIs and BDZs both in short-term and in long-term studies (Berger et al. 2004, Kipper et al. 2007, Massion et al. 2002, Reich 2003, Roy-Byrne et al. 2003, Slaap and den Boer 2001). Possible explanations for the negative effect of axis-II comorbidities on the outcome of treatment could include the absence of adherence to treatment regime or a difficulty in establishing the therapeutic alliance.

Moreover, a longer duration of illness and an early onset were found to predict non-response in the long-

term treatment studies (Kipper et al. 2007, Slaap and den Boer 2001). On the other hand, there is evidence that being in good physical conditions and an earlier administration of medications could be slight positive predictors of response to therapy (Pollack et al. 2002, Roy-Byrne et al. 2003). Furthermore, demographical predictors such as sex, age and marital status have not been shown to significantly influence treatment outcome of PD patients, regardless of used drugs (Kipper et al. 2007, Slaap and den Boer 2001). However, it was found that a higher economical status could be a weak positive predictor of response to paroxetine (Roy-Byrne et al. 2003) and that poorer people could be more likely to be non responsive to therapy (Roy-Byrne et al. 2006). Among psychosocial factor, personality traits were found to influence treatment response as well. In particular, higher harm-avoidance and neuroticism seem to be the most important predictors of non-response to therapy, whereas higher self-directedness, agreeableness and cooperativeness could predict a god response to drug (Carrera et al. 2006, Marchesi et al. 2006a).

In conclusion, although a large number of predictors have been identified, the effect that each single predictor could have on treatment outcome is usually small. Furthermore, taking into account the low number of studies specifically concerned with such topic, there is not yet sufficient evidence to determine whether data observed in relationship with specific drugs can be generalized to other drugs. Also, because the maiority of current studies were limited by the lack of placebo or active comparator control group, it is not possible to draw definitive conclusions as to whether observed effects are specifically attributable to specific pharmacological compounds or, more broadly, represent predictors of such non specific factors as positive expectancy and medical care.

Treatment resistant Panic Disorder

In spite of the availability of treatments for PD patients, about 20% to 40% of such patients do not respond, or only partially respond to first line treatments (Bandelow and Ruther 2004). When the initial treatment fails, the physician should consider a change of the dose or a switch to another treatment modality. Although some reviews suggest that dose increase is an efficient strategy in the management of resistance, there are no controlled studies that support this procedure for treatment resistant PD. Furthermore, first line pharmacological treatments could be augmented by means of additional drugs, or by means of other treatment modalities. Furukawa et al. investigated the incremental effect of combined psychotherapy (most often CBT) and antidepressant treatment in a systematic review including 21 trials (Furukawa et al. 2007). The authors concluded that, in the short term, combined therapy was superior to medication alone, as well as to psychotherapy alone. Furthermore, the augmentation of a second drug with a different mechanism of action is recommended for patients with partial response to SSRIs and SNRIs, whereas in subjects who do not respond to first line agents, the most successful strategy could be to switch the drug being used with an antidepressant presenting a different mechanism of action (Ipser et al. 2006).

On the basis of current evidence, international guidelines suggest that when initial treatments have failed, and the drug has been increased to the highest tolerated dose, patients should first be switched to another SSRI or to an SNRI. The next step should be the switch to a TCA. Then, BDZs, MAOIs, and the RIMA moclobemide should be tried. Last, drugs or drug combinations that showed efficacy in open studies and in case reports could be considered, prioritizing those agents for which there is a larger availability of data.

In addition, anticonvulsants may be considered as monotherapies or adjunctive pharmacological options for PD when patients have failed to response to several standard treatments as well (Van Ameringen et al. 2004). Small open trials concerning valproate (Baetz and Bowen 1998, Primeau et al. 1990, Woodman and Noyes 1994), vigabatrin (Zwanzger et al. 2001) and levetiracetam (Papp 2006) have been published with positive results. Pertaining to valproate, a double blind placebo controlled study (Lum 1990) also showed that this mood stabilizer could have anti-panic properties and could be safe and well tolerated. Conversely, the gabaergic anticonvulsants gabapentin and tiagabine have not showed significant advantages over placebo (Pande et al. 2000, Zwanzger et al. 2009).

Note also that in a relevant proportion of cases, resistance to antidepressant treatment might be related to comorbid bipolarity (Keck et al. 2006, Perugi et al. 2010). Perugi et al. found that valproate was an effective and well-tolerated adjunctive treatment in PD patients who were either resistant to antidepressant therapy or had comorbid bipolar disorder. Moreover, patients with co-occurring PD and bipolar disorder should be generally treated with a mood stabilizing medication before considering the addition of an antidepressant (Keck et al. 2006). Indeed, the use of antidepressants could increase the number of panic attacks that, in bipolar patients, could simply reflect a symptom of excitement. In conclusion, antiepileptic drugs may have a place in PD treatment. Nevertheless, further investigation is needed to determine under what circumstances they should be used as monotherapy or as augmenting agents in individuals who are partially or non responsive to conventional therapies.

Finally, other pharmacological options have been suggested for PD treatment in addition to drugs mentioned above. These include pindololo (Hirschmann et al. 2000) as well as the antipsychotics aripiprazole (Pae et al. 2008, Worthington et al. 2005), risperidone (Simon et al. 2006) and olanzapine (Hollifield et al. 2005, Sepede et al. 2006). However, future research is needed to clarify the role of antipsychotics in PD treatment, especially if one considers the risk of severe adverse effects associated with such drugs.

Conclusion

PD is a prevalent and disabling chronic illness that is frequently associated with other comorbidities and with a significant reduction of the quality of life. Although several evidence-based treatments for PD are currently available, only a minority of patients affected

by PD are adequately treated. The first-line pharmacotherapies for PD are SSRIs and venlafaxine. Adjunctive short-term treatment with a BDZ may be useful, as SSRIs and SNRIs may take time to lead to therapeutic benefits. TCAs and MAOIs should be considered as an alternative choice only when patients do not seem to respond to or tolerate the first-line treatment. Recently, novel antidepressant drugs with different mechanism of actions have been suggested for PD treatment as well, although they are not sufficiently investigated by means of well-designed randomized controlled clinical studies thus far.

A critical evaluation of current guidelines, however, points to the dearth of information as to which pharmacological compound can be best tailored to the specific need of each individual patient. On the basis of reviewed data, the extent to which different antidepressants vary in terms of efficacy and tolerability is unclear. Therefore, more information is needed to provide clinicians with a useful tool for guiding clinical choices on the basis of rigorous empirical evidence and for possibly enhancing treatment outcomes.

Our findings point to the need for more rigorous and properly powered double blind head to head comparison trials that could provide more reliable information as to how different medications differ in terms of effectiveness and tolerability for PD treatment. Other important issues that should be taken in account in future studies are greater sample size and the application of more sensitive instruments of evaluation of the outcomes. Working in this direction, more significant information about differences between drugs could be obtained. At the same time, further research should be carried out to identify subgroups of patients who could benefit from specific treatments based on biological and psychological characteristics, so as to develop differential indications for each specific subgroup of patients.

Furthermore we underscore that objective risks and benefit of each therapeutic option should be particularly taken into account into the development of an optimal therapeutic plan for PD patients so as to reduce dropout rates and increase treatment adherence. Another crucial issue is the optimal duration of pharmacotherapy that could allow patients to discontinue medications without risks of relapse. On account of the limited available empirical data, most guidelines suggest continuation for at least 1 year. Further research on the optimal duration of pharmacotherapy should be conducted, as well as research on how treatment adherence can be optimized.

Concerning refractory PD, novel treatment modalities with little evidence to date can also be considered. As an example, anticonvulsants and atypical antipsychotics could be considered. However, more rigorous placebo-controlled studies are needed to better clarify the role of such therapeutic options, particularly taking into account their side effect profile. Finally, we underscore that a better knowledge about the neurobiological dysfunction underlying PD, complemented with the study of genetically controlled variations in drug response, could help clinicians to better target symptoms with the appropriate pharmacological agents and could also be useful in developing new drugs.

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