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Novel Antidepressants and Panic Disorder: Evidence beyond Current Guidelines

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Key Words
Panic disorder · Mirtazapine · Reboxetine · Milnacipran · Duloxetine

Abstract
Aim: The aim of the present review is to summarize available evidence about the efficacy and side effects of novel antidepressants for the treatment of panic disorder. ***Methods:*** A literature search was undertaken using MEDLINE, ISI web of knowledge and references of retrieved articles. The search included articles published in English up to September 2009. Both controlled and uncontrolled trials were included. The quality of the reviewed articles was also assessed. ***Results:*** Fourteen mainly poor-quality studies were included. Mirtazapine showed some efficacy in reducing the number and the severity of panic symptoms in many uncontrolled studies and was comparable to selective serotonin reputake inhibitors (SSRIs) in direct-comparison studies. Reboxetine was significantly more efficacious than placebo but less effective than SSRIs. Further uncontrolled studies suggested preliminary evidence for the use of milnacipran and duloxetine as well. All drugs were usually well tolerated. ***Discussion:*** Current studies do not yet provide convincing evidence supporting the efficacy of mirtazapine, reboxetine, milnacipran and duloxetine for the treatment of panic disorder patients. However, on account of positive preliminary results, further research is warranted.

Introduction

Panic disorder (PD) is a common chronic and often disabling illness [1] which affects >5% of the population at some point in life and is associated with increased use of health care and reduced workplace productivity [2].

Pharmacological treatments approved by current guidelines including Australian (last update 2003) [3], World Council of Anxiety (last update 2003) [4] and American Psychiatric Association (last update 2009) [5] guidelines for the treatment of PD comprise tricyclic antidepressants, benzodiazepines, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs) and venlafaxine. With little differences among guidelines, SSRIs and venlafaxine are considered first-line agents for PD patients [3–5] because they are described as having the most favourable balance of efficacy and side effects. The use of benzodiazepines for the long term is not recommended due to the high likelihood of depen-

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dence and withdrawal and because their use as needed could interfere with psychological approaches such as cognitive behavioural therapy and enhance the anticipatory fear cycle (e.g. [6]). Despite the great number of pharmacological options, however, less than a half of the patients suffering from PD experience a full and sustained remission [2].

While early drugs mainly focused on the role of the serotonergic system which is disrupted in PD [7], in the last decade novel antidepressant drugs (NAD) targeting also noradrenaline, such as venlafaxine, have begun to be explored in the treatment of PD patients with positive results [8]. The aim of the present review is to summarize available evidence about the efficacy and side effects of further NAD including mirtazapine [9], duloxetine [10], milnacipran [11] and reboxetine [12] not yet approved by current pharmacological guidelines for the treatment of PD.

Methods

A literature research was undertaken using MEDLINE, ISI web of knowledge, the Cochrane collaboration database and references of retrieved articles. The search included papers published in English up to September 2009. The main search terms were panic disorder, mirtazapine, reboxetine, duloxetine and milnacipran in various combinations as needed.

All studies indexed by the electronic databases mentioned above focusing on the efficacy and tolerability of NAD for PD were screened independently by 2 reviewers in order to be considered for the inclusion. Included studies had to: (1) investigate PD patients (age 18–75 years) with or without further comorbidities; (2) use NAD not yet approved by guidelines for the treatment of PD, and (3) provide quantitative measures about the efficacy and/or tolerability of such drugs. Case reports and review articles were excluded. The original search identified >50 eligible articles, among which 14 could be included (table 1).

The main considered outcome measures were: (1) absolute and relative number of responders (as defined by the authors' criteria) of patients treated with NAD compared to those treated with placebo or with different antidepressants, and (2) side effect profile related to NAD. The data were extracted independently by 2 reviewers. The quality of controlled studies was assessed using the Jadad Scale [13] and that of uncontrolled studies with the Newcastle-Ottawa Scale [14] (table 2). For controlled trials, a score ≥ 3 was considered to be indicative of a high-quality study [13], whereas for uncontrolled ones, a score ≥ 4 was considered as suggestive of high quality [14].

Results

A summary of the included studies with details is reported in tables 1 and 2.

Mirtazapine

Mirtazapine is a noradrenergic and specific serotonergic antidepressant that enhances noradrenergic transmission via blockade of α_2-adrenoceptors [9] and enhances serotonergic transmission via noradrenergic stimulation of α_1-adrenoceptors and blockade of α_2-heteroreceptors [15] which already showed efficacy for major depression (MD) [16] and anxiety disorders [17].

Uncontrolled Studies. In a first case series, very good response rates were found [18]. Similar results were observed in a following study [19] in a larger sample. The analyses also showed a consistent reduction in many psychological scales such as the Hamilton scale for depression (HAM-D) [20] ($p < 0.005$) and the 90-item symptom checklist [21] ($p < 0.001$). Despite both studies being limited by the use of concomitant benzodiazepines, a following study [22] in 15 patients not allowing any drug other than mirtazapine observed significant improvements as well. Further uncontrolled research confirmed these findings in 2 independent samples with comorbid MD [23, 24].

Comparison with Active Treatments. In a first high-quality study [25] in 27 patients randomly assigned to mirtazapine or fluoxetine, both treatments showed significant and comparable efficacy. In a further nonrandomized trial [26] comparing mirtazapine with paroxetine, both treatments were associated with significant and comparable reductions in symptoms, with maintenance of the effect 6 months later [26]. Note, however, that the apparent lack of differences between mirtazapine and active comparators could be linked to the small sample size of both studies which did not enable to detect small statistical differences between groups.

Safety and Tolerability. The most commonly reported side effects (>10%) related to mirtazapine were drowsiness [19, 25, 26], weight gain [19, 25, 26], blurred vision [25], increased appetite [19], muscle pain [19] and tiredness [19]. Further side effects (<10%) were apathy and headache [25]. No significant difference was found between mirtazapine and SSRIs, apart from a significantly higher rate of weight gain in mirtazapine groups [25, 26]. Sexual dysfunction was not assessed in any study. Less than 10% of the patients treated with mirtazapine discontinued the trials prematurely, particularly because of weight gain [19, 25, 26], excessive sedation and headache [24].

Reboxetine

Reboxetine is a selective noradrenaline reuptake inhibitor which has no significant effects on histaminergic,

Table 1. Overview of included studies

Study	Drug (dosage)	Subjects (ITT)	Comorbid agora-phobia	Duration of trial (days)	Study design	Comorbid-ities	Concomitant therapies	Re-sponse	Definition of response	Main side effects (>25%)
Carpenter et al. (1999) [18]	mirtazapine (median 30)	10	9	112	UCT	GAD	BDZ and SSRIs (doses not specified)	7/10	final CGI-I scores ≤2	weight gain and somnolence
Ribeiro et al. (2001) [25]	mirtazapine (18.3 ± 1.3)	14	9	56	RCT	none	none	–	–	headache and drowsiness for both drugs; weight gain for mirtazapine
	fluoxetine (14 ± 1)	13	10							
Boshuisen et al. (2001) [19]	mirtazapine (15–60)	23	12	84	UCT	none	oxazepam (max. 20 mg <4 days a week)	20/23	final CGI-I scores ≤2	drowsiness and weight gain
Carli et al. (2002) [22]	mirtazapine (30)	15	4	72	UCT	none	none	–	–	dry mouth and drowsiness
Ilies-Alexandru and Zaharia (2002) [23]	mirtazapine (31.66)	54	–	84	UCT	MD	none	44/54	final CGI-I scores ≤2	–
Sarchiapone et al. (2003) [24]	mirtazapine (30)	45	14	84	UCT	MD	benzodiazepines (low doses not specified)	41/45	decrease >50% in PDSS scores	none
Montañes-Rada et al. (2005) [26]	mirtazapine (30)	36	27	56	CT	GAD, MD, dysthymia	lorazepam or bromazepam (once a day, max. 3 mg)	22/31	no panic attack during the last week of the study	weight gain for mirtazapine
	paroxetine (20–30)	26	16					19/24		
Versiani et al. (2002) [29]	reboxetine (6–8)	37	–	56	RCT	none	benzodiazepines (daily, low doses not better specified)	–	–	headache, tachy-cardia, constipa-tion, dry mouth and constipation comparable in both groups
	placebo	37	–							
Dannon et al. (2002) [30]	reboxetine (8)	24	13	36	UCT	none	none	–	–	none
Seedat et al. (2003) [32]	reboxetine (8–10)	13	17 (in total)	56	RCO	not acute dysthymia or anxiety disorders	none	7/13	final CGI-I scores ≤2	insomnia for re-boxetine, nausea and decreased libido for citalo-pram, and dry mouth for both
	citalopram (20–60)	9						9/11		
Bertani et al. (2004) [33]	reboxetine (8)	34	23	90	RCT	none	none	12/27	reduction >50% in both PASS-total and SDS-total	dry mouth and sweating for rebox-etine, sexual side effects and weight gain for paroxetine
	paroxetine (40)	34	22					24/30		
Cia et al. (2006) [36]	milnacipran (100)	74	–	63	UCT	MD	clonazepam (0.5–2 mg/day)	–	–	none
Simon et al. (2009) [41]	duloxetine (60–120)	15	6	63	UCT	MD, dysthymia or other anxiety disorders	low-dose benzodiazepines	8/15	final PASS scores = 0	none

Dosage = Range in flexible-dose studies and final value in fixed-dose studies when available, otherwise mean value: all measures are expressed in milligrammes. Response = Usually measured as CGI-I score 1 or 2; details in the text. ITT = Intent to treat; UCT = uncontrolled trial; RCT = randomized controlled trial; RCO = randomized crossover trial; MD = major depression; GAD = generalized anxiety disorder; CGI-I = clinical global impression for improvement; PASS = panic-associated symptom scale; SDS = Sheenan disability scale; PDSS = panic disorder severity scale; BDZ = benzodiazepines; – = not specified.

Table 2. Quality of included studies

a Controlled trials

Study	Randomization	Appropriate randomization	Dropouts and withdrawals	Blinding	Appropriate blinding	Jadad score
Ribeiro et al. (2001) [25]	yes	yes	yes	yes	unclear	4
Versiani et al. (2002) [29]	yes	unclear	yes	yes	unclear	3
Seedat et al. (2003) [32]	yes	unclear	yes	yes	no	2
Bertani et al. (2004) [33]	yes	yes	yes	yes	no	3
Montañes-Rada et al. (2005) [26]	no	–	yes	yes	no	1

b Uncontrolled trials

Study	Representativeness	Adequate ascertainment of treatment	Assessment of outcome	Adequate follow-up duration	Adequacy of follow-up	Newcastle-Ottawa Scale score modified
Carpenter et al. (1999) [18]	no	unclear	yes	yes	yes	3
Boshuisen et al. (2001) [19]	yes	unclear	yes	yes	no	3
Carli et al. (2002) [22]	yes	unclear	yes	yes	yes	4
Ilies-Alexandru and Zaharia (2002) [23]	no	unclear	yes	yes	unclear	2
Sarchiapone et al. (2003) [24]	no	unclear	yes	yes	yes	3
Dannon et al. (2002) [30]	yes	unclear	yes	no	yes	3
Cia et al. (2006) [36]	no	unclear	yes	no	no	1
Blaya et al. (2007) [37]	no	unclear	yes	yes	yes	3
Simon et al. (2009) [41]	no	unclear	yes	yes	yes	3

cholinergic and adrenergic receptors [27] and showed significant efficacy for MD [28].

Placebo-Controlled Studies. In a single randomized study [29], reboxetine showed significantly higher efficacy as compared to placebo. However, a significant limitation of the study was the concomitant use of benzodiazepines.

Evidence from Uncontrolled Studies. In a following uncontrolled trial [30], a similar significant reduction in panic symptoms was measured at the end of the study. Furthermore, significantly higher reductions at the end point were observed in the 11 patients without compared to the 13 patients with comorbid agoraphobia in the Hamilton scale for anxiety (HAM-A) and HAM-D, suggesting both a possible efficacy of reboxetine in previous treatment-resistant patients and a possible higher efficacy in patients without comorbid agoraphobia. A further study investigating the effects of 7 days of treatment with paroxetine or reboxetine on the reactivity to inhalations of 35% carbon dioxide/65% oxygen [31] found that patients treated with paroxetine showed a larger reduction in the reactivity to CO_2, possibly suggesting higher importance of the modulation of the serotonergic system in PD patients.

Comparison with Active Treatments. In a first randomized crossover study [32], although reboxetine and citalopram were found to be equally effective in reducing the severity of panic attacks from baseline, citalopram was associated with a significantly higher rate of response. In a second higher-quality study comparing reboxetine to paroxetine [33], the number of responders was significantly higher in the paroxetine group.

Safety and Tolerability. The most commonly reported side effects (>10%) related to reboxetine were nausea [32, 33], tachycardia, constipation, drowsiness, decreased appetite, blurred vision [29], dry mouth, sweating, headache and insomnia [29, 32, 33]. Further side effects (<10%) were palpitations [30, 33], tremors [29, 33], insomnia and urinary retention [30]. No sexual dysfunction or weight gain, associated with SSRI treatment, were found in patients receiving reboxetine [32, 33]. Less than 5% of the patients treated with reboxetine dropped out for side effects [29, 32].

Milnacipran

Milnacipran is a dual serotonin and noradrenaline reuptake inhibitor virtually equipotent in terms of its ability to inhibit both the noradrenaline and serotonin uptake pumps [34] particularly used for the treatment of MD [35].

Evidence from Uncontrolled Studies. In an early uncontrolled study on 73 PD patients [36], 85% of the participants showed a significant response to this drug at the end point and 70% were free from full panic attacks. In a following study [37], however, only 18 out of 31 patients responded. The authors noted that this response rate was significantly lower than that observed with tricyclics and SSRIs for PD [38] and they suggested that it could be imputed to the higher selectivity of milnacipran for noradrenaline as compared to serotonin.

Safety and Tolerability. Major side effects (>10%) related to milnacipran were constipation, hot flashes, nausea, anxiety, tiredness, agitation, sweating, headache, abdominal pain, nervousness, dry mouth, sexual dysfunction, insomnia, somnolence, palpitation, tremors and vomiting [36, 37]. The treatment was well tolerated with only 4 patients discontinuing because of adverse events [36, 37].

Duloxetine

Duloxetine is a potent dual reuptake inhibitor of both serotonin and noradrenaline which lacks significant affinity for histamine H1, α-adrenergic, dopamine D2 and serotonin receptors [39] particularly used for the treatment of MD [40].

Evidence from Uncontrolled Studies. A single study [41] on 15 subjects suggested that duloxetine could reduce symptoms' severity, with 8 patients not experiencing full panic attacks in the past 2 weeks and 4 achieving full remission.

Safety and Tolerability. The side effects experienced by at least 10% but <25% of the subjects reported in the study by Simon et al. [41] included: constipation, dry mouth, nausea, headache, sexual dysfunction, urinary hesitation, insomnia and sedation. Only 2 patients discontinued the trial because of side effects.

Conclusion

Our review of antidepressants not yet approved by current pharmacological guidelines for the treatment of PD evidenced an almost complete lack of double-blind placebo-controlled studies investigating this issue. Even though a paucity of trials aiming at exploring the usefulness of such drugs for PD patients was somewhat expected, otherwise they could be included in recently published guidelines of the American Psychiatric Association [5], the paucity of large uncontrolled studies, small randomized controlled studies as well as long-term studies was unexpected, as the majority of such drugs has been available since the late 1990s.

Major evidence derives from 7 studies focusing on mirtazapine, some of which suggested similar efficacy as compared with paroxetine and fluoxetine, 2 SSRIs commonly used for PD. However, such studies were characterized by many methodological shortcomings including the absence of a placebo control group, a small sample size which did not enable to detect more subtle differences between mirtazapine and active comparators, and the frequent use of concomitant drugs already known to be efficacious for the treatment of PD. Reboxetine was the only drug to be found significantly more efficacious than placebo, though less efficacious than SSRIs. Further uncontrolled studies suggested that milnacipran and duloxetine could have some efficacy for PD patients as well, although the absence of placebo-controlled studies does not allow to clarify the magnitude of the specific effects of such drugs as compared to placebo or even to the natural course of illness. Also, the only study investigating the long-term effects of mirtazapine suggested that 94% of the patients who responded in the short term did not relapse at the 6-month follow-up [26], a percentage substantially greater than in the existing literature on other agents [42], raising concerns about the reliability of these findings.

All drugs were usually well tolerated and the side effects reported in patients with PD were consistent with those mentioned in the literature from properly powered double-blind randomized controlled studies in patients suffering from MD [43–47]. Furthermore, reboxetine and duloxetine showed no and few effects, respectively, on sexual function, suggesting their potential usefulness for patients who complain of this side effect usually associated with SSRIs [48]. However, none of the included studies investigated sexual dysfunction by means of specific sexual questionnaires, a considerable issue given that patients, if not directly questioned, tend to underreport such side effects (e.g. [49]).

Eventually, comparing the absolute response values of these drugs to those reported in the literature for SSRIs and venlafaxine, we observed that, despite the dual mechanisms of action of most reviewed drugs, their efficacy does not seem superior to that of commonly used drugs

for PD [50, 51], leading to the hypothesis that both serotonin and noradrenaline could act as parts of a more complicated network of interactions which is likely to include dopamine [52, 53] and GABA [54] as well. Accordingly, preliminary evidence suggests that antipsychotics and anticonvulsants could be useful for the treatment of PD [55], but it is too soon to reach definitive conclusions.

Many limitations should be considered in the interpretation of the reviewed findings, comprising the small sample size of many included studies, often linked to type 1 errors (false-positive findings), the use of concomitant drugs with established efficacy for the treatment of PD and the inclusion of patients with several comorbidities. Also, no comparison with placebo is available for mirtazapine, milnacipran and duloxetine, and the use of different criteria for the evaluation of symptom reduction and, particularly, clinical response does not allow precise comparisons across the studies. However, on account of positive findings suggesting significant effects of NAD in PD patients, further studies using clearer and more standardized criteria as well as including placebo control groups and long-term data are warranted.

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