Anticonvulsant and antipsychotic medications in the pharmacotherapy of panic disorder: a structured review

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Abstract

Background: As the remission rate of panic disorder (PD) achieved with conventional pharmacotherapy ranges between 20% and 50%, alternative psychopharmacological strategies are needed. We aimed to firstly review data regarding use of antipsychotic and non-benzodiazepine anticonvulsant medication in PD patients with or without comorbidities; secondly, to review data concerning reduction of panic symptoms during treatment of another psychiatric disorder with the same medications; and thirdly, to examine reports of anticonvulsant- or antipsychotic-induced new-onset panic symptomatology.

Methods: We performed a PubMed search (last day: 28 April 2020) of English-language studies only, combining psychopathological terms (e.g. 'panic disorder') and terms referring either to categories of psychotropic medications (e.g. 'anticonvulsants') or to specific drugs (e.g. 'carbamazepine'). All duplications were eliminated. All studies included in the review met certain inclusion/exclusion criteria. The level of evidence for the efficacy of each drug was defined according to widely accepted criteria.

Results: In treatment-resistant PD, beneficial effects have been reported after treatment (mostly augmentation therapy) with a range of anticonvulsant (carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, valproate, vigabatrin, tiagabine) and antipsychotic (aripiprazole, olanzapine, risperidone, sulpiride) medications: overall, most medications appear generally well tolerated. Additionally, bipolar patients receiving valproate or quetiapine-XR (but not risperidone or ziprasidone) demonstrated reductions of comorbid panic-related symptoms. There are case reports of new-onset panic symptoms associated with clozapine, haloperidol, olanzapine and topiramate, in patients with conditions other than PD. The small-to-modest sample size, the lack of control groups and the open-label and short-term nature of most of the reviewed studies hinder definitive conclusions regarding either the short-term and long-term efficacy of antipsychotic and anticonvulsant medications or their potential long-term side effects.

Conclusion: Some atypical antipsychotic and anticonvulsant medications may have a role in the treatment of some PD patients, mostly when more conventional approaches have not been successful, but the quality of supporting evidence is limited.

Keywords: anticonvulsants, antipsychotics, medication, panic disorder, pharmacotherapy

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Introduction

Panic disorder: clinical features, prevalence, etiology

Panic disorder (PD) is a psychiatric disorder characterised by recurring panic attacks – brief periods of severe psychological and somatic symptoms of anxiety, typically peaking within 10 min and resolving within 30 min – at least some of which are, or have been, unexpected. Between panic attacks, the patient is relatively free from panic psychopathology. However, patients demonstrate

concern, worry and/or behavioural changes due to anticipation of future panic attacks. There is a substantial overlap between PD and agoraphobia.[1] PD is often comorbid with other psychiatric syndromes, including other anxiety disorders, major depression and bipolar disorder.[2] Comorbidity of PD with depression is particularly common and results in greater impairment and increased use of health services.[3] Lifetime prevalence of PD ranges from 1% to 3% in the general population, while the prevalence in clinical settings ranges from 3.0% to 8.3%. Furthermore, PD and other anxiety disorders contribute to approximately 1% of all disability-adjusted life years, and 3.5% of all years lived with disability worldwide.[4] The exact pathogenesis of PD remains uncertain, but a range of biological and psychosocial factors contribute to the emergence and maintenance of panic psychopathology.[5–10]

PD: current standard treatment modalities and their efficacy

Significant progress has been achieved concerning the presumed biological basis[8,11] and the pharmacotherapy of PD.[3,12] Selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) are commonly recommended first-line and second-line pharmacotherapies, followed by a number of switching strategies, while cognitive-behaviour therapy (CBT) is the first-line psychological treatment.[3,12] However, a significant proportion of PD patients shows little or no response to standard pharmacotherapies, CBT and/or their combination, and suffer from significant and impairing residual symptoms. The remission rates achieved with pharmacotherapy range between 20% and 50%, and approximately 20% of patients will remain substantially impaired despite undergoing a succession of pharmacological and/or psychosocial treatments.[13,14] Therefore, PD is considered a potentially chronic, recurrent and often difficult-to-treat psychiatric illness.

Despite the official guidelines, which consider pharmacotherapy with antidepressants alone and CBT alone as two treatment modalities with similar efficacy, some research data suggest that psychopharmacological treatment may be somewhat more effective than psychotherapies – including CBT – especially for more severely ill patients with PD without or with agoraphobia (PDA). It remains uncertain whether combined CBT-pharmacotherapy is substantially more effective than either approach given as monotherapy.[12,15,16] There is a need for novel interventions that might enable non-responders or partial responders to become full-responders to treatment. Drugs with proven efficacy and acceptability in patients with other psychiatric conditions might conceivably be suitable for 'repurposing' in patients with treatment-resistant PD.

Rationale for the use of anticonvulsants in treating PD

Benzodiazepines modulate brain levels of γ-aminobutyric acid (GABA), which is implicated in the pathogenesis of PD and other anxiety disorders, but they are not considered a first-line pharmacotherapy due to their adverse effects, including abuse liability, withdrawal symptoms and memory deficits.[3] Early theoretical views stressed that anticonvulsants possess GABAergic properties but lack the adverse effects of benzodiazepines, and this advantage could support the use of the former instead of the latter in panic and anxiety states.[17,18] A strong indication that anticonvulsants could be an efficacious substitute for benzodiazepines is that some of them, e.g. pregabalin and tiagabine,[19–22] may sometimes be helpful in discontinuing long-term benzodiazepine use and ameliorating associated memory deficits.[23] Biological mechanisms included in a 'kindling' model may be important in the pathogenesis of PD,[24] and anticonvulsants may have a particular role in the pharmacotherapy of PD.

The GABA-A receptor subtype regulates excitability and acute changes in fear/anxiety responses to exteroceptive or interoceptive stimuli.[25] Abnormal GABA activity may contribute to the pathophysiology of PD; for example, a PET study suggests that PD patients demonstrate decreased GABA-A receptor binding.[26] The main mode of action of anticonvulsant drugs is the elevation of GABA brain levels by inhibiting the GABA-catabolising enzyme GABA-transaminase.[17] This GABAergic action of anticonvulsants was the decisive reason for exploring their potential utility to treat PD and other anxiety disorders.[24] Additionally, anticonvulsants exert their action through a regulating effect on excessive sodium and calcium fluxes (e.g. carbamazepine, valproate, lamotrigine and phenytoin) and/or through the modulation of serotonin (valproate and lamotrigine), dopamine (valproate), noradrenaline (lamotrigine) and hypothalamic-pituitary activity (lamotrigine).[24,25]

During a panic attack, a strong association with the surrounding context is established, suggesting that the hippocampus and other structures of the 'fear circuit' may be critically involved in the pathophysiology of PD, given their role in contextual processing.[6,27] Anticonvulsants probably act by regulating the malfunctioning of this fear circuit. For example, Santos *et al.* reported that administration of tiagabine – a GABA reuptake inhibitor – significantly reduced hippocampal hyperexcitability and abnormal fear circuit activation in an animal model of panic/fear.[27] Moreover, the 'kindling model' (originally developed to explain progression of epilepsy) may also apply to the pathogenesis of panic. More precisely, theoretical views stress that repetitive activation and kindling of brain structures involved in fear responses, such as the amygdala and the hippocampus, may result in excitatory output similar to that observed in epilepsy. Therefore, anticonvulsant medication could exert a therapeutic action by limiting this excessive activation.[24] In line with this notion, an investigation using an animal model of limbic epilepsy, provides evidence for a bidirectional, mutually exacerbating effect of epilepsy and panic-like behaviours in animals: animals were subject to alternating electrical stimulations of the basolateral amygdala (BLA) to induce kindling of limbic seizures, and of the dorsal periaqueductal grey (DPAG) to induce panic-like episodes; BLA-DPAG stimulation exacerbated panic-like episodes more drastically than DPAG stimulation alone, but BLA stimulation alone was not panicogenic.[28]

Rationale for the use of antipsychotics in treating PD

PD and other anxiety disorders are often comorbid with psychotic disorders,[29] while apparently psychosis-like features can sometimes be seen as part of the clinical presentation of PD and other anxiety disorders.[30–33] For example, panic attacks during adolescence were associated significantly with increased levels of psychotic-like psychopathology among young adults.[34] In a previous study in 35 medication-free, acutely ill patients with PD (29 with comorbid agoraphobia) without a history of psychosis, significant correlations emerged between the Symptom Checklist-90-Revised (SCL-90-R) 'psychoticism' and 'paranoid ideation' subscales and the study's clinical measures of panic psychopathology; the authors suggested that PD patients can be differentiated according to the severity of their 'psychoticism' as a dimension, comprising clinical features such as psychotic-like experiences, increased social alienation, hostility and suspiciousness, and concluded that these associations may reflect a more severe subtype of PD.[32] Finally, there is evidence for the efficacy of antipsychotic drugs in reducing anxiety psychopathology in psychotic patients.[35,36]

Previous researchers have explored the potential utility of antipsychotic medications in anxiety disorders. In earlier times, patients with 'anxiety neuroses' were frequently treated with 'typical' high- or low-potency antipsychotics, including haloperidol, flupenthixol, chlorprothixene, melperone and others at lower doses that those used for the treatment of patients with schizophrenia. However, anxiety disorders, including PD, run a chronic course and often need long-term pharmacotherapy. Therefore, concerns regarding typical antipsychotics' tardive adverse effects led to the abandonment of these pharmacological strategies.[37] With the advent of second generation antipsychotics (SGAs), researchers returned to investigate whether these 'atypical' antipsychotics could prove both efficacious in treatment-resistant PD and other anxiety disorders and better tolerated, since they lack some of the more serious adverse effects of typical antipsychotics.[38]

Fear- and anxiety-conditioning animal models are used to explore whether antipsychotic drugs attenuate anxiety/fear responses acquired through learning mechanisms.[39,40] Data from experiments in rats (passive- and active-avoidance conditioning models) suggest that the atypical antipsychotics olanzapine and clozapine possess anxiolytic properties that are not attributable to this antipsychotic effect, or to their effects on motor functions or learning and memory processes; by contrast, haloperidol did not possess anxiolytic properties in these particular conditioning models, but demonstrated an anxiogenic-like activity.[40]

Data from animal studies suggest positive correlations between panic/fear/anxiety manifestations and release of dopamine in certain brain structures, including the prefrontal cortex and the amygdala.[41–44] Dopamine contributes significantly to the modulation of a 'cortical brake' that the medial prefrontal cortex exerts on the panicogenic/anxiogenic activity of the amygdala, and influences the impulse trafficking between the basolateral and central nuclei of the amygdala.[45] D1- and D2-dopamine receptors in the amygdala have different roles in the modulation of anxiety:

D1 receptors participate in danger recognition facilitating conditioned–unconditioned associations by the retrieval of the affective properties of the unconditioned stimuli, and in the control of impulse trafficking from cortical and basolateral regions and central nuclei, respectively, whereas D2 receptors generate adaptive responses to cope with aversive environmental stimuli.[45]

The potential anti-panic properties of antipsychotics in humans may be due to their direct action in dopaminergic systems.[46] Antipsychotic drugs – both typical and atypical – block the acquisition of conditioned fear responses.[39,47,48] SGAs are agonists of $5HT_{1A}$ receptors and/or antagonists of $5HT_{2A}$ and $5HT_{2C}$ receptors,[13,49] which are implicated in the neurobiology of PD, since they mediate the activation of the amygdala,[50] which is considered the central neuronal structure of the 'fear circuit'.[6,7] For example, the possible anti-panic effects of olanzapine may be due partly to its $5HT_{1A}$ agonist properties,[51] and of risperidone to its antagonistic properties at $5HT_{2A}$ receptors.[52–54] The anti-panic effects of SSRIs may be due partly to the blockade of excitatory $5HT_{2A}$ receptors located on inhibitory GABA inter-neurons, suppressing the firing of noradrenergic neurons in the locus coeruleus.[55,56] This may explain the anti-panic properties of SGAs: for example, the affinity of risperidone for the $5HT_{2A}$ receptor is greater than its affinity for the D2 receptor.[46,57] Overall, the anti-panic effect of SGAs may be due to their dual action in suppressing both dopaminergic and serotonergic activity. Additionally, in the cerebral cortex and the hippocampus of rodents, olanzapine and clozapine seem to increase levels of the neuroactive steroid allopregnanolone, a potent GABA-A receptor modulator that possesses anxiolytic-like properties.[58,59]

Aims of the review
A number of reports – mainly case reports and open-label studies – have described the potential utility of anticonvulsant and antipsychotic medications in PD patients who have not responded to standard anti-panic pharmacological and psychosocial treatments, and who do not suffer from major psychiatric comorbidities. A number of previous review papers concerning the pharmacotherapy of PD in general, also include data with respect to the administration of antipsychotic or anticonvulsant medications.[3,12,16,60,61] A number of previous papers have specifically reviewed the administration either of anticonvulsant drugs,[4,25]

or of antipsychotic medications,[46,59,62–66] in the pharmacotherapy of PD. The most recent of these reviews date back to 2008 regarding anticonvulsant drugs,[24] and to 2016 concerning antipsychotic medications.[59]

Subsequently, an updated review of data concerning the use specifically of antipsychotic and anticonvulsant drugs in the treatment of PD is the main aim of the present report.

We also aimed to review data from previous reports of the administration of an anticonvulsant or antipsychotic medication for the treatment of another psychiatric disorder (e.g. bipolar disorder) with comorbid panic psychopathology.

Finally, we wished to examine reports of newly onset panic symptomatology after the administration of an anticonvulsant or an antipsychotic medication given for another psychiatric condition.

Method for the literature review

Criteria for appraisal of quality of reports
A PubMed search was conducted to answer the three research questions mentioned above in *Aims of the study*. Subsequently, a number of general and specific inclusion/exclusion criteria were used to decide whether to include a report in our review.

General inclusion/exclusion criteria. The following inclusion and exclusion criteria had to be met for a study report or a letter to be included in the present review:

General inclusion criteria
(1) The report must have been published only in a scientific journal with a peer-review process; (2) the diagnostic procedures, pharmacotherapy and clinical follow up were all conducted by psychiatrists; and (3) the diagnosis was based on criteria from standard, broadly accepted international diagnostic systems (DSM, ICD).

General exclusion criteria
(1) The study sample included patients with comorbid major somatic diseases, including epilepsy; (2) the study's sample included patients with comorbid alcoholism and/or other substance abuse disorders, except smoking; (3) presence of ethical issues.

Inclusion/exclusion criteria regarding the first research question. Regarding our main aim, i.e. to review studies that have explored the potential utility of anticonvulsant and antipsychotic medications in PD patients who have not responded to standard anti-panic treatments, the following inclusion/exclusion criteria had to be met for a study to be included in the present report:

Inclusion criteria: (1) the study sample included patients suffering primarily from PD with or without agoraphobia, according to DSM-5 or ICD-10 diagnostic criteria; (2) all the 'general inclusion criteria' had to be met.
Exclusion criteria: (1) the study sample included patients with comorbid major psychiatric disorder (e.g. schizophrenia, bipolar disorder, etc.); (2) patients in the study suffer from panic attacks or other panic/agoraphobic symptoms, but these did not meet the DSM/ICD criteria for PD/PDA; (3) all the 'general exclusion criteria' had to be met.

Inclusion/exclusion criteria regarding the second research question. Regarding our second research aim, i.e. to review data from previous reports of the administration of an anticonvulsant or an antipsychotic medication for the treatment of another psychiatric disorder (e.g. bipolar disorder) with comorbid panic psychopathology, the following inclusion/exclusion criteria had to be met for a study to be included in the present report:

Inclusion criteria: (1) the study sample included patients suffering primarily from another psychiatric disorder for which they receive the anticonvulsant or antipsychotic medication (e.g. bipolar disorder, psychosis) and either (a) from comorbid DSM/ICD PD/PDA, or (b) from comorbid panic attacks and other panic/agoraphobic symptoms, which yet did not meet the DSM/ICD diagnostic criteria for PD/PDA; (2) all the 'general inclusion criteria' had to be met.
Exclusion criteria: all the 'general exclusion criteria' had to be met.

Inclusion/exclusion criteria regarding the third research question. Regarding our third aim, i.e. to review data from reports of newly onset panic symptomatology after the administration of an anticonvulsant or an antipsychotic medication, given for another psychiatric condition, all the 'general inclusion/exclusion criteria' had to be met for a study to be included in the present report.

Search terms – search methodology and results

Anticonvulsants. We performed an updated PubMed search using the terms ('panic disorder', OR 'agoraphobia', OR 'panic disorder'-AND-'agoraphobia', OR 'panic attacks', OR 'panic') AND ('anticonvulsants' OR, 'antiepileptics', OR 'carbamazepine', OR 'gabapentin', OR 'lamotrigine', OR 'levetiracetam', OR 'phenobarbital', OR 'phenytoin', OR 'pregabalin', OR 'tiagabine', OR 'topiramate', OR 'valproate', OR 'vigabatrin') (the anticonvulsant medications are named in alphabetical order). The PubMed search concerned only non-benzodiazepine anticonvulsant medications.

More precisely, the term 'antiepileptics' was combined with the terms 'panic disorder' ($N = 395$) and 'agoraphobia' ($N = 101$) (in brackets the number of papers that the respective search yielded). Moreover, the term 'antiepileptics' was also combined with the more 'general' terms 'panic attacks' ($N = 420$) and 'panic' ($N = 478$) so as to trace papers possibly missing from the first two searches.

Likewise, the term 'anticonvulsants' was combined with the terms 'panic disorder' ($N = 387$) and 'agoraphobia' ($N = 97$). Moreover, the term 'anticonvulsants' was also combined with the more 'general' terms 'panic attacks' ($N = 409$) and 'panic' ($N = 471$) so as to trace papers possibly missing from the first two searches.

The searches in PubMed combining each of the terms 'panic disorder'/'agoraphobia'/'panic attacks'/'panic' with specific drugs (e.g. 'carbamazepine', 'lamotrigine', etc.) did not add any further reports to those already found when categories of drugs were investigated ('antiepileptics', etc.).

The abstracts (as demonstrated in the PubMED platform) of all papers yielded by the above mentioned searches were screened so that reports that did not relate to the study aims and inclusion/exclusion criteria were rejected and duplications were not taken into consideration.

The last day of the PubMed search was the 28 April 2020. Only studies in the English language were reviewed.

Antipsychotics. We performed an updated PubMed search using the terms ('panic disorder',

OR 'agoraphobia', OR 'panic disorder'-AND-'agoraphobia', OR 'panic attacks', OR 'panic') AND ('antipsychotics', OR 'neuroleptics' OR 'second-generation antipsychotics', OR 'amisulpride', OR, 'aripiprazole', OR 'clozapine', OR 'haloperidol', OR 'olanzapine', OR 'risperidone', OR 'sulpiride', OR 'trifluoperazine', OR 'ziprasidone') (the antipsychotic medications are named in alphabetical order).

More precisely, the term 'antipsychotics' was combined with the terms 'panic disorder' ($N=215$) and 'agoraphobia' ($N=40$) (in brackets the number of papers which the respective search yielded). Moreover, the term 'antipsychotics' was also combined with the more 'general' terms 'panic attacks' ($N=240$) and 'panic' ($N=260$) so as to trace papers possibly missing from the first two searches.

Likewise, the term 'neuroleptics' was combined with the terms 'panic disorder' ($N=191$) and 'agoraphobia' ($N=39$). Moreover, the term 'neuroleptics' was also combined with the more 'general' terms 'panic attacks' ($N=205$) and 'panic' ($N=236$) so as to trace papers possibly missing from the first two searches.

Additionally, the term 'second generation antipsychotics' was combined with the terms 'panic disorder' ($N=26$) and 'agoraphobia' ($N=5$). Moreover, the term 'second generation antipsychotics' was also combined with the more 'general' terms 'panic attacks' ($N=26$) and 'panic' ($N=28$) so as to trace papers possibly missing from the previous two searches.

The searches in PubMed combining each of the terms 'panic disorder'/'agoraphobia'/'panic attacks'/'panic' with specific antipsychotic drugs (e.g. 'risperidone, 'haloperidol' etc.) did not add any further reports to those already found when categories of drugs were investigated ('antipsychotics', etc.).

The abstracts (as demonstrated in the PubMed platform) of all the papers yielded by the above mentioned searches were screened, so that reports which did not relate to the study's purpose and inclusion/exclusion criteria were rejected and duplications were not taken into consideration.

The last day of PubMed search was the 28 April 2020. Only studies in the English language were reviewed.

Criteria for the levels of evidence

We used the following internationally used criteria concerning levels of evidence[3,25,67]: level 1 = meta-analysis of randomised controlled trials (RCTs); level 2 = at least one RCT; level 3 = uncontrolled trial with ⩾10 subjects; and level 4 = anecdotal case reports.

Anticonvulsants

Anticonvulsants in patients with a primary diagnosis of PD, or without other comorbid psychiatric conditions

The following anticonvulsants (in alphabetical order) have been used in patients with a primary diagnosis of PD, or PD without comorbidities (Table 1):

Carbamazepine. An early open-label study suggested a possible anti-panic effect of carbamazepine.[69] Subsequently, a controlled study explored the potential efficacy of carbamazepine (mean dose = 679 mg/day; mean treatment duration = 66 days) in the treatment of 14 PD patients.[68] Despite improvement in anxiety symptoms on several measures, only one patient demonstrated a marked and sustained clinical improvement while taking carbamazepine. The presence of either abnormalities in the electroencephalogram (EEG) or prominent psycho-sensory symptoms did not predict response to carbamazepine. Subsequently, there is level 3 evidence that carbamazepine administration may have some short-term benefits. Other studies have explored the efficacy of carbamazepine more systematically in treating 'panic attacks' in non-epileptic patients with various psychiatric disorders demonstrating abnormal EEGs (see for a review, see Boutros *et al.*[83]). Further data concerning these studies are reported below.

Gabapentin and pregabalin. Gabapentin and pregabalin are structurally related compounds classified as γ-aminobutyric analogues or gabapentinoids, which have broadly similar pharmacodynamic properties. Although both compounds are structurally related to GABA, neither has affinity for GABA receptors: instead, they exert their action through binding to the a2-δsubunit of voltage-gated calcium channels in the central nervous system and the resulting inhibition of neuronal signaling.[84]

In an 8-week, double-blind clinical trial, 133 PD patients received either gabapentin (600–3600 mg/

Table 1. Administration of anticonvulsant drugs in patients with a primary diagnosis of PD, or without other comorbid psychiatric conditions (anticonvulsants in alphabetical order; studies for the same drug in chronological order).

Authors	Anticonvulsant drug	Type of trial	Duration of trial	Number of PD patients	Dosage	Outcome	Comments
Uhde et al.[68]	Carbamazepine	Controlled study	Mean = 66 days	14	Mean dose = 679 mg/day	Improvement in several measures, but only 1 patient demonstrated marked and sustained improvement.	EEG abnormalities and prominent psycho-sensory symptoms did not predict response.
Tondo et al.[69]	Carbamazepine	Open-label	52 weeks	34	Mean dose = 419 mg/day	58% improved	
Lum et al.[70]	Divalproex sodium	Placebo-controlled	6 weeks	12	Dosage titration according to response and side-effects.	Significant reductions of panic attack intensity/duration.	But improvements were evident only when sodium divalproex was administered as a first medication.
Woodman and Noyes[71]	Divalproex sodium	Open-label	6 weeks	12	Starting-dose = 500 mg/day; upward titration according to response/side-effects.	All patients completed the trial; all were moderately-to-markedly improved.	11 patients continued divalproex-treatment and retained therapeutic gains at 6-month follow up.
Baetz and Bowen[72]	Divalproex sodium	Open-label	8 weeks	10	Flexible-dose to achieve serum levels = 45–90 µg/ml.	All patients improved significantly regarding panic attacks' frequency, 'mood instability', and depressive/anxiety symptoms.	
Pande et al.[73]	Gabapentin	Double-blind, placebo-controlled	8 weeks	133	600–3600 mg/day	Overall, active treatment was not better than placebo. But active treatment was better than placebo only concerning the more severe cases (especially females).	Gabapentin monotherapy trial.
Joos and Zeeck[74]	Gabapentin	Case-report	7 weeks	1	1800 mg/day	Reductions of PDA symptoms already from the 1200 mg/day.	Gabapentin monotherapy (given initially for phantom-pain). Titration: first 3 weeks 1200 mg/day and then increased to 1800 mg/day due to pain persistence.

(Continued)

Table 1. (Continued)

Authors	Anticonvulsant drug	Type of trial	Duration of trial	Number of PD patients	Dosage	Outcome	Comments
Masdrakis et al.[75]	Lamotrigine	Open-label	14 weeks	4	200 mg/day	Significant improvement of patient under monotherapy; some improvement in 2 other patients (chronic severe agoraphobia).	Monotherapy = one patient; augmentation therapy = three patients. Titration: slowly during the first 6 weeks. Concomitant medication: paroxetine (three patients), clomipramine (1) and alprazolam.[2] All medication dosages remained steady ≥3 months before intake and during the trial. Higher dosages might be needed for severe PD/PDA cases. Meticulous follow up for potential Stevens–Johnson syndrome.
Papp[76]	Levetiracetam	Open-label	12 weeks	18	500 mg/day	13 completed; 11 = 'very much' or 'much' improved	Adverse effects: sedation, headache and irritability.
Windhaber et al.[77]	Oxcarbamazepine	Case-report	6 months	1	900 mg/day	Remission of panic symptoms 2 weeks after increase of oxcarbazepine dosage to 900 mg/day.	Oxcarbazepine (600 mg/day) was administered for two alcohol-induced seizures; 2 weeks later panic attacks emerged, which remitted after oxcarbazepine increase to 900 mg/day. No re-emergence during next 6 months.
Zwanzger et al.[18]	Tiagabine	Open-label	4 weeks	4	15 mg/day	Marked improvement of panic and agoraphobia.	In two of the four patients remission was achieved after 4 weeks of treatment. Prior to trial, three patients were treatment-resistant and one was drug-naïve. One patient improved but discontinued tiagabine after 2 weeks due to side-effects.
Sheehan et al.[78]	Tiagabine	Open-label	10 weeks	28	Mean dose = 15.1 mg/day (range = 4–20 mg/day).	Statistically significant but clinically non-significant symptom reductions (25–32%).	Adverse events: nausea, dizziness and headaches. Many drop-outs (N = 5) due to side-effects.

(Continued)

Table 1. (Continued)

Authors	Anticonvulsant drug	Type of trial	Duration of trial	Number of PD patients	Dosage	Outcome	Comments
Zwanzger et al.[79]	Tiagabine	Double-blind, placebo-controlled	4 weeks	19 active treatment = 10; placebo = 9	Up to 30 mg/day	Clinical improvement: tiagabine was not superior to placebo. But CCK-4 challenges (after 2 and 4 weeks of treatment): significantly less tiagabine-patients panicked compared with placebo-patients.	Tiagabine may reduce sensitivity to panicogenic stimuli. Patients were medication-free ≥10 days before intake. Starting-dose = 5 mg; individually increased to maximum 15 mg/day (1st week) and 30 mg/day (weeks 2–4). Higher dosages and longer duration of treatment may be needed.
Primeau and Fontaine[62], Primeau et al.[80]	Valproate	Open-label	7 weeks	10	Up to 2250 mg/day	Significant improvement of panic attacks and global psychopathology but not of phobic anxiety.	1 week of placebo-washout prior to valproate administration. Starting dose = 500 mg/day; increase by 250 mg every second day, up to 2250 mg/day according to response and tolerance. One drop-out due to side-effect (heartburn). Frequent adverse-effects: nausea, dizziness, drowsiness and tremor.
Ontiveros and Fontaine[81]	Valproate sodium-clonazepam combination	Case-report	4-month to 2-year follow up.	4	Valproate: 1250–2000 mg/day; Clonazepam: 2–6 mg/day.	Clinically significant improvements retained during follow up.	Three patients were much more improved after valproate was added to clonazepam initial therapy. A fourth patient had a history of alcohol and benzodiazepines abuse. In all cases, relapses occurred when clonazepam dosage was reduced after initial response.
Keck et al.[82]	Valproate	Open-label	4 weeks	14	20 mg/kg/day	10 patients (71%): >50% reduction in panic attack frequency; four patients: complete remission. And lactate challenge: 10 out of the 12 valproate-treated baseline-panickers (83%) did not panic at post-treatment.	Patients remained drug-free for 30 days prior to valproate administration.
Zwanzger et al.[17]	Vigabatrin	Open-label	4 weeks; 6 months follow up	3	2 g/day	Marked reductions of panic symptoms. Two patients (67%): rapidly panic-free; remained so during the 6-month trial.	Meticulous follow up needed for potential visual field constrictions after long-term treatment.

CCK-4, cholecystokinin-4; EEG, electroencephalogram; PD, panic disorder; PDA, panic disorder with agoraphobia.

day) or placebo.[73] Overall, no significant difference between active treatment and placebo was observed. However, when the data from only the more severely patients [panic and agoraphobia scale (PAS) score > 20] were taken into consideration, significantly greater reductions in the PAS score were achieved by gabapentin-treated patients, especially female patients. In a subsequent case report of a 43-year-old male with a 10-year long history of PD with severe agoraphobia, gabapentin was administered for comorbid phantom pain after finger amputation, and titrated up to 1800 mg/day: incidentally, panic and agoraphobic symptoms were reduced significantly, re-emerging after a 6-day cessation of treatment, but remitting again after gabapentin was reintroduced.[74] Overall, there is level 2 evidence that severely ill PD patients, especially females, may benefit from therapy with gabapentin. Although pregabalin has efficacy in generalised anxiety disorder (GAD),[21] there is no report as yet regarding the potential efficacy and safety of pregabalin either as monotherapy or as augmentation therapy in the treatment of PD.

Lamotrigine. In an open-label, fixed-dose (200 mg/day), 14-week trial, lamotrigine was administered either as an augmentation therapy (three patients with chronic and severe agoraphobia) or as monotherapy (one drug-naïve patient with first-onset PDA).[75] Lamotrigine was slowly titrated up to 200 mg/day within 6 weeks and maintained at that dosage for a further 8 weeks. Patients underwent follow up every week. The patient under lamotrigine monotherapy improved significantly, whereas two of the other patients improved to some extent. However, all patients who underwent augmentation with lamotrigine demonstrated chronic and severe agoraphobia (a robust predictor of pharmacotherapy-resistance).[85] Higher dosages might be needed in such cases, in line with data suggesting improvement of post-traumatic stress disorder with lamotrigine dosages up to 500 mg/day.[86] The clinician must be aware of safety issues, especially the risk of severe skin eruptions: slow titration of medication and careful monitoring of patients decreases this risk – a procedure that was followed strictly in this study.[75] To the best of our knowledge, no other report has explored the pharmacotherapy of PD with lamotrigine. Consequently, there is level 4 evidence that lamotrigine may have some benefits in PDA patients.

Levetiracetam. This antiepileptic drug modulates high-voltage, N-type, voltage-dependent calcium channels and potassium currents: it is uncertain whether it potentiates GABA-A-mediated activity, and it may act through modulation of synaptic vesicle protein 2A involved in vesicle exocytosis.[25,61] In a 12-week, open-label, fixed-flexible dose clinical trial, levetiracetam was administered to 18 PD/PDA patients: 13 completed the study and 11 were 'very much' or 'much' improved [Clinical Global Impression-Improvement scale (CGI-I)], most within the first weeks of treatment, and levetiracetam was well tolerated with minimal side effects.[76] Consequently, there is level 3 evidence that levetiracetam may alleviate panic-related symptoms.

Oxcarbamazepine. Only one case report has explored the administration of oxcarbazepine in PD[77]: a 23-year-old male demonstrated persistent multiple panic attacks and anticipatory anxiety while receiving oxcarbazepine 600 mg/day for alcohol-related grand-mal seizures. A diagnosis of PD was made and oxcarbazepine was increased to 900 mg/day. Panic symptomatology remitted within the first 2 weeks and did not re-emerge for the next 6 months of treatment. Consequently, there is level 4 evidence that oxcarbazepine may alleviate panic symptoms.

Topiramate. To the best of our knowledge, the potential utility of topiramate in the treatment of PD has not been evaluated. However, the emergence of new-onset panic attacks during therapy with topiramate for conditions other than PD has been reported,[87–89] as described in a subsequent section.

Valproate. Valproate enhances GABA activity in the brain, has anxiolytic-like effects in animal models of anxiety, and may have utility in humans.[82] Valproate blocks voltage-dependent sodium channels and T-type calcium channels, and possesses strong GABAergic potency due to direct action at GABA-B receptors, causing an increase in brain GABA.[25] This GABA-ergic activity of valproate seems to significantly contribute to its psychotropic effect.[25] Early case reports suggested the potential usefulness of valproate in the treatment of PD comorbid with other clinical entities, including benzodiazepine withdrawal,[90] alcoholism and affective disorders,[91] substance abuse,[92] and multiple sclerosis.[93]

In an early study, 10 PD patients underwent 7 weeks of treatment with valproic acid up to 2250 mg/day: patients showed significant improvements in panic attacks and overall clinical

presentation, but not in phobic anxiety: the most frequent adverse effects included nausea, dizziness, drowsiness and tremor.[62,80] Subsequently, in a placebo-controlled 6-week trial of sodium divalproex in 12 PD patients, a significant reduction in the intensity and duration of panic attacks was observed: these improvements were evident only in patients receiving sodium divalproex as a first medication.[70] In another study, four treatment-resistant PD patients improved significantly when they received a sodium valproate-clonazepam combination, but relapses occurred when clonazepam dosage was reduced.[81] Keck *et al.* explored whether 28 days of valproate treatment (20 mg/kg/day) blocked lactate-induced panic attacks in 14 PD patients who underwent lactate infusion-challenge pre- and post-treatment[82]: 10 patients (71%) demonstrated a significant reduction (>50%) in panic attack frequency and the remaining 4 patients had complete remission. Furthermore, valproate blocked re-induction of panic symptoms on post-treatment lactate infusion in 10 out of the 12 patients (83%) who had panicked at the pre-treatment lactate challenge.

In a 6-week, open-label clinical trial, 12 PD patients received divalproex sodium with a starting dose of 500 mg/day and upward titration according to clinical response and side-effects: all patients completed the trial and all were moderately-to-markedly improved, panic and anxiety psychopathology improved faster and more robustly compared with agoraphobia, and 11 patients elected to continue treatment with divalproex and retained therapeutic gains at 6-month follow up.[71] Additionally, in an 8-week, open-label, flexible-dose (so as to achieve serum levels of 45–90 μg/ml) trial, divalproex sodium was administered in 10 PD patients with comorbid 'mood instability', all previously resistant to pharmacotherapy and CBT: all patients demonstrated significant improvements regarding number of panic attacks, 'mood instability' and depressive and anxiety symptoms.[72] Overall, there is level 3 evidence that valproate may effectively reduce PD symptoms.

Vigabatrin and tiagabine. Vigabatrin (γ-vinyl-GABA) is an irreversible inhibitor of GABA-transaminase, which increases brain and cerebrospinal fluid GABA levels by two- to threefold in experimental animals and humans.[94] Three severely ill PD patients without psychiatric comorbidities demonstrated marked reductions of panic psychopathology after a 6-month vigabatrin administration (2 g/day): two patients were free of panic attacks after just a few days of treatment and remained panic-free during the 6-month trial.[17] Consequently, there is level 4 evidence that vigabatrin alleviates PD symptoms. Clinicians must meticulously evaluate the patient for the potential occurrence of visual field constrictions after long-term administration of vigabatrin: data from epileptic patients suggest that a daily dose of 1500 g or more increases the risk of significant visual field defects.[95]

Tiagabine, a selective GABA-reuptake inhibitor, exerts its action through blockade of GABA transporter-I, which enhances GABA reuptake: the resulting strengthening of inhibitory GABAergic neurotransmission in various brain systems accounts for both its anti-epileptic and anti-anxiety clinical efficacy.[22] Case reports suggest some efficacy as an augmentation therapy in obsessive-compulsive disorder and in the discontinuation of long-term benzodiazepine abuse.[22,96] In healthy volunteers, administration of either vigabatrin or tiagabine reduced cholecystokinin-4 (CCK-4)-induced panic and anxiety manifestations to an extent similar to that achieved by alprazolam.[97,98] Tiagabine has more limited effects compared with vigabatrin, although some researchers suggest slow titration to a daily dosage above the standard ones (30 mg/day) may boost therapeutic gains.[99] Zwanzger *et al.* were the first to administer tiagabine (15 mg/day) to four PD patients in a 4-week trial[18]: three patients were treatment-resistant and one was drug-naïve. Three patients demonstrated marked improvements in both panic and agoraphobic symptoms: the fourth patient improved but tiagabine had to be discontinued after 2 weeks of treatment due to side-effects (sedation and severe vertigo). In a subsequent open-label study, PD/PDA patients aged 18–64 years received tiagabine (mean dose = 15.1 mg/day; range = 4–20 mg/day) for 10 weeks: reductions between 25–32% were observed across all outcome measures, but they were not considered clinically significant by the researchers. Tiagabine was generally well tolerated, the most common adverse events being nausea, dizziness and headaches. Only one patient discontinued tiagabine due to adverse events.[78] Another study that explored the potential benefit of a 4-week pharmacotherapy with tiagabine up to 30 mg/day in 19 PD patients (active treatment = 10; placebo = 9) included a panic-inducing challenge (CCK-4) (performed twice, after 2 and 4 weeks of therapy, respectively) to further evaluate potential anti-panic effects: tiagabine was not superior to placebo regarding symptom reduction, although subjects treated with

tiagabine showed significantly less panic responses to the administration of CCK-4 compared with placebo-treated patients, suggesting that tiagabine may reduce patients' sensitivity to panicogenic stimuli.[79] Therefore, there is level 3 evidence that tiagabine is not superior to placebo regarding PD symptom reduction, although it may reduce patient sensitivity to panicogenic stimuli.

Anticonvulsants in non-epileptic patients with PD, and in patients with 'panic attacks' and abnormal EEG

Boutros *et al.* reviewed data concerning the efficacy of anticonvulsants in treating psychopathological manifestations in non-epileptic patients with various psychiatric disorders and demonstrating abnormal EEGs.[63,83] Altogether, eight reports were found concerning patients suffering from 'panic attacks'. One was the above-mentioned study by Uhde *et al.*,[68] which was the only one that included patients with PD (and not simply with 'panic attacks') and that suggested that carbamazepine had no efficacy in PD, irrespective of the presence or absence of EEG abnormalities. The remaining descriptions are either single case reports,[100–103] or case-series.[104–106] All patients in these studies underwent EEG and received carbamazepine either as monotherapy or in combination with other antiepileptics or benzodiazepines. Overall, Boutros *et al.* stressed that no definitive conclusions could be drawn regarding the usefulness of anticonvulsant drugs in patients with 'panic attacks' demonstrating abnormal EEGs,[83] as the results varied between no treatment gains,[106] and response only when a combination of antiepileptic drugs was administered.[101,105]

Administration of anticonvulsants in patients with comorbid panic and bipolar disorders

In a study of 47 PD patients with comorbid bipolar disorder ($N=35$) or who were 'otherwise resistant to antidepressants' ($N=12$) involving adjunctive pharmacotherapy with valproate (mean dose = 687 mg/day; range: 400–1500 mg/day), all antidepressant-resistant patients and 88.6% of patients with bipolar comorbidity achieved symptom remission: during a 3-year follow-up period, 58.3% of antidepressant-resistant subjects and 48.6% of bipolar patients had a relapse of PD after remission. The authors concluded that, in some PD patients, resistance to antidepressants is due mainly to co-occurring 'mood instability', and speculated that PD is likely to be a heterogeneous disorder, including a sub-group of patients who respond better to valproate.[107]

New-onset panic attacks as an adverse effect of anticonvulsant administration

Topiramate is a fructopyranose sulfamate anticonvulsant that blocks sodium and γ-amino-3-hydroxy-5-methylisoxazole-4-propionic acid/kainite N-methyl-d-aspartate receptors.[87] Three case reports have previously reported topiramate-induced panic attacks.[87–89] Goldberg described the emergence of new-onset panic attacks in a 24-year-old female with comorbid bipolar-II and binge-eating disorders, after augmenting lamotrigine with topiramate aiming at both weight loss and mood stabilisation.[87] Panic attacks resolved after termination of topiramate treatment, but re-emerged after topiramate re-administration. Possibly, the carbonic-anhydrase properties of topiramate may lead to carbon dioxide retention, which triggers panic manifestations.[87] A case report described a 27-year-old female patient with bipolar-II disorder without history of panic manifestations who, after switching from lithium to topiramate, demonstrated panic attacks at the 150 mg/day dosage (titration lasted 6 weeks). At 2 weeks after discontinuing topiramate, panic symptoms completely remitted; subsequent re-administration of topiramate for hypomania resulted in re-emergence of panic symptoms, which again resolved after the drug's termination and did not appear again during the 4-month follow up.[88] In another case report, a 17-year-old patient with borderline personality disorder suffered from panic attacks after topiramate 25 mg/day was added to a 5-month treatment with escitalopram (10 mg/day) and interpersonal psychotherapy: the possible causal relationship between topiramate and panic attack emergence was supported by the cessation of panic attacks following drug discontinuation and their re-emergence after drug resumption.[89]

Antipsychotics

Administration of antipsychotics in patients with a primary diagnosis of PD, or without other comorbid psychiatric disorders

Two reports have described the administration of olanzapine and sulpiride, respectively, as monotherapy in treatment-resistant PD patients without comorbidities.[14,108] One case report describes the administration of aripiprazole monotherapy in a SSRI-resistant PD patient with comorbid major depression.[109] All other reports describe the utility

of antipsychotic medications as augmentation therapy to extant treatment. The potential effectiveness of antipsychotic drug monotherapy in the treatment of acute panic symptomatology is unknown.[64] The following antipsychotics (in alphabetical order) have been used in PD with or without psychiatric comorbidities (Table 2):

Aripiprazole. A retrospective study explored the efficacy and safety of augmentation therapy with aripiprazole (16.9 ± 6.6 mg/day; range 7.5–30 mg/day) in 17 SSRI-resistant patients, including 11 patients with anxiety disorders (with two PD patients) and 6 patients with depression: up to 59% of subjects demonstrated significant clinical improvements (CGI-I ⩽ 2), but up to 29% of the patients discontinued treatment – 18% due to side-effects. Although the results suggested a beneficial effect of augmentation therapy with aripiprazole, there was no mention of the clinical course of the two PD patients, or whether they were among the drop-outs.[38] Harada *et al.* described the case of a 36-year-old PDA patient who improved significantly after a 4-month treatment with paroxetine 40 mg/day,[13] but with persistent limited-symptom attacks and agoraphobic avoidance: augmentation of paroxetine with aripiprazole 6 mg/day was associated with rapid (within 1 week) and marked improvement in panic and agoraphobic features, the therapeutic gains being maintained over a 4-month follow up, with no serious adverse effects.

In an 8-week, flexible-dose, open-label trial, Hoge *et al.* administered augmentation therapy with aripiprazole in 10 PD patients (5 with comorbid GAD) resistant to at least 8 weeks of standard pharmacotherapy,[110] using a flexible-dosage protocol starting at 2.5 mg/day and titrated up to 30 mg/day based on response and tolerability (mean dosage = 10.5 ± 4.95 mg/day). Augmentation with aripiprazole significantly reduced anxiety and depressive symptoms and improved the overall clinical presentation [Clinical Global Impression-Severity scale (CGI-S)], but only one patient (10%) achieved remission (CGI-S ⩽ 2). Up to 30% of patients discontinued treatment prematurely: adverse effects included sedation, fatigue, insomnia, jitteriness, dyspepsia and nausea. The authors conclude that aripiprazole may be an effective and well-tolerated augmentation strategy in pharmacotherapy-resistant PD.[110] Overall, there is level 3 evidence that aripiprazole may be beneficial in the treatment of PD as augmentation therapy.

Additionally, in a case report of a treatment-resistant patient with PD comorbid with major depression, who underwent monotherapy with aripiprazole titrated up to 10 mg/day, panic and depressive symptoms were significantly improved within the first 6 weeks of therapy. Moreover, magnetic resonance imaging (MRI) structural analysis revealed that, within this 6-week period of treatment with aripiprazole, a growth in grey matter and brain volume increase had occurred.[109]

Olanzapine. Augmentation with olanzapine may be beneficial in pharmacotherapy-resistant PD. This was first evaluated in two PD patients.[50] The first patient (a 32-year-old man) was switched from perphenazine (15 mg/day) to olanzapine (12.5 mg/day) and from venlafaxine (150 mg/day) to nefazodone (600 mg/day); 4 months later, panic attacks and agoraphobia had fully remitted. Nevertheless, the comorbid psychiatric disorder is not reported (hospitalised for 'suicidal thoughts' shortly before olanzapine administration), while the simultaneous administration of nefazodone may have contributed significantly to symptom remission. The second patient (a 40-year-old woman) suffered from treatment-resistant 'panic attacks with agoraphobia' without comorbidities. She was switched from perphenazine (12 mg/day) to olanzapine 10 mg/day, while amitriptyline (75 mg/day) and diazepam (10 mg/day) were reduced during the trial. Panic and agoraphobic psychopathology improved within 2 weeks and remitted within 2.5 months.

A subsequent report described two female patients with treatment-resistant PDA (one with no comorbidity, the other with comorbid recurrent major depression); in both cases, rapid (within the first days) improvement in panic manifestations was observed after adding olanzapine (5 mg/day) to paroxetine (40 mg/day).[51] Likewise, augmenting paroxetine with olanzapine resulted in complete remission of panic psychopathology in a 49-year-old man.[111]

Among 10 treatment-resistant PD patients who completed an 8-week, open-label, flexible-dose, clinical trial of olanzapine monotherapy (mean dose = 12.1 mg/day; dose range = 2.5–20 mg/day), up to 50% were panic-free and 40% reported only one panic attack during the previous week, while in 60% anticipatory anxiety completely remitted.[108] A wash-out (2–5 weeks) of all medications preceded the trial. Weight gain was observed in 60% of patients (0.18 ± 4.4 kg). The

Table 2. Administration of antipsychotic drugs in patients with a primary diagnosis of PD, or without other comorbid psychiatric conditions (antipsychotics in alphabetical order; studies for the same drug in chronological order).

Authors	Antipsychotic drug	Type of trial	Duration of trial	Number of PD patients	Dosage	Outcome	Comments
Hoge et al.[110]	Aripiprazole	Open-label	8 weeks	10	Mean dosage = 10.5 ± 4.95 mg/day	Significant improvements regarding panic, anxiety, depression and overall clinical presentation.	Augmentation in treatment-resistance. Up to 30% of patients prematurely discontinued treatment. Adverse events: sedation, fatigue, insomnia, jitteriness, dyspepsia, nausea.
Harada et al.[13]	Aripiprazole	Case-report	4 months	1	6 mg/day	Rapid and marked improvement - maintained during the trial of both residual panic symptoms and paroxetine-resistant agoraphobia.	Augmentation with aripiprazole (6 mg/day; no titration) of a 4-month paroxetine-treatment (40 mg/day; both prior and during the trial). No serious adverse events.
Lai[109]	Aripiprazole	Case-report	6 weeks	1	10 mg/day	Significant reductions in both panic and comorbid depression.	Aripiprazole monotherapy. Abrupt switch from a 4-month escitalopram-therapy (20 mg/day) to aripiprazole 5 mg/day, titrated to 10 mg/day within 2 weeks. MRI: grey matter growth and brain volume increase.
Etxebeste et al.[50]	Olanzapine	Case-report	4 and 2.5 months respectively.	2	12.5 mg/day and 10 mg/day respectively.	Significant reductions in both panic and agoraphobia.	Augmentation in pharmacotherapy-resistant patients. Patient-1 was hospitalised for 'suicidal thoughts' shortly before the trial. Olanzapine (titrated to 12.5 mg/day after 2 weeks) replaced perphenazine. During the trial nefazodone replaced venlafaxine and two benzodiazepines were stopped. Patient-2 received olanzapine-augmentation of a 5-month amitriptyline-diazepam combination (both were reduced during the augmentation trial).
Khaldi et al.[51]	Olanzapine	Case-report	–	2	5 mg/day	Rapid reduction of panic.	Augmentation in non-response to paroxetine (40 mg/day).
Chao[111]	Olanzapine	Case-report	–	1		Complete remission of panic symptoms.	Augmentation of paroxetine with olanzapine.
Hollifield et al.[108]	Olanzapine	Open-label	8 weeks	10	Mean-dose = 12.1 mg/day	Significant reductions of panic attacks and anticipatory anxiety (panic-free = 50%).	Augmentation in pharmacotherapy-resistance. In eight patients, psychotropic drugs were tapered off over a 2- to 5-week period before olanzapine administration. Medications remaining during the trial in the other two patients are not reported. Weight gain = 0.18 ± 4.4 kg.

(Continued)

Table 2. (Continued)

Authors	Antipsychotic drug	Type of trial	Duration of trial	Number of PD patients	Dosage	Outcome	Comments
Sepede et al.[112]	Olanzapine	Open-label	12 weeks	26	5 mg/day	'Response' = 81.8% 'Remission' = 57.7%. Response = CGI-I ≤ 2 + ≥50% reduction of panic attacks. Remission = no panic attacks and HAM-A ≤ 7 at end-point.	Augmentation in treatment-resistance to 11.1 ± 3.4 weeks of pharmacotherapy with paroxetine 40 mg/day (N = 27) or sertraline 150 mg/day (N = 4). Medications remained stable during augmentation-trial. Adverse events: mild-to-moderate weight gain and drowsiness.
Goddard et al.[113]	Quetiapine-XR	Double-blind, placebo-controlled, randomized, parallel-group	8 weeks	21 Quetiapine = 10; placebo = 11	150 ± 106 mg/day	No significant differences between quetiapine-XR and placebo.	Augmentation in SSRIs-resistance. Patients with some other psychiatric and/or other medical conditions were not excluded. Not a unified definition of 'SSRI-resistance' used in the study.
Simon et al.[114]	Risperidone	Open-label	8 weeks	7 (and 23 with other anxiety disorders)	1.12 ± 0.68 mg/day. (mean dose concerning all 30 patients)	PD subgroup: significant reductions of PDA symptoms and overall clinical improvement.	Augmentation in chronic treatment-refractory anxiety disorders. Adverse events: sedation/fatigue, appetite increase, weight gain, dizziness.
Prosser et al.[115]	Risperidone versus paroxetine	Randomized, rater-blind	8 weeks	56 (PD = 43; major depression and panic attacks = 13)	Mean dosage of risperidone = 0.53 mg/day (range = 0.125–1.0 mg). Paroxetine = 30 mg/day (fixed-dose).	Significant reduction of panic attacks' frequency/severity. Efficacy: risperidone = paroxetine.	Augmentation in treatment-resistance. Attrition rate = 48% (risperidone = 39.4%; paroxetine = 60.9%; no statistical difference). Paroxetine was initiated without titration. Concomitant medication not reported; but (a) the use of antipsychotics and any changes in antidepressant or mood stabilizer dosages during the 2 months prior to study and (b) the use of other psychotropic drugs during the study were both exclusion criteria.
Nunes et al.[14]	Sulpiride	Open-label	8 weeks	19	100, 150, or 200 mg/day, according to symptoms' severity.	Significant improvement: panic attacks (panic-free) = 63.2%); anxiety; overall clinical presentation.	Sulpiride monotherapy of treatment-resistant PD. One-week wash-out period (paroxetine, citalopram, or sertraline) prior to sulpiride administration. Most common adverse events (mild severity): appetite change, amenorrhea/galactorrhea.

CGI-I, clinical global impression of improvement; HAM-A, Hamilton anxiety rating scale; MRI, magnetic resonance imaging; PD, panic disorder; PDA, panic disorder with agoraphobia; SSRI, selective serotonin re-uptake inhibitors.

authors concluded that olanzapine is potentially effective and safe to administer to PD patients, taking into consideration the limitations of a case-series report.

In a 12-week, open-label study, 26 PD patients with SSRI-resistance received augmentation therapy with olanzapine (fixed-dose: 5 mg/day)[112]; 21 (81.8%) were 'responders', and 57.7% (N = 15) achieved 'remission'. The most frequent adverse effects were mild-to-moderate weight gain and drowsiness. The authors concluded that olanzapine may successfully augment SSRIs in treatment-resistant PD and, since SSRI-treatment was either paroxetine or sertraline, speculated that the positive effect of olanzapine augmentation was due to pharmacodynamic rather than pharmacokinetic factors. Overall, there is level 3 evidence that olanzapine may be an effective augmentation strategy for the treatment of non-responders to standard anti-panic pharmacotherapy.

Quetiapine. In a double-blind, placebo-controlled, randomised, parallel-group, 8-week clinical trial, PD patients with SSRI-resistance underwent augmentation with quetiapine-extended release (XR).[113] Response was defined as ⩾50% decrease in the Panic Disorder Severity Scale (PDSS); 10 quetiapine-treated (150 mg ± 106 mg/day) and 11 placebo-treated completed the trial. Quetiapine-XR was well tolerated, but was not better than placebo in reducing panic psychopathology. The study's main limitations included the small sample size, the relatively low mean dose of quetiapine-XR and the non-exclusion of patients with comorbid psychiatric (except psychosis or bipolar disorder) and/or other medical comorbidities (except if they were unstable). Notably, there were no unified criteria for the definition of 'SSRI-resistance'. Thus, medication-free patients at intake underwent an 8-week SSRI-treatment and were characterised as 'treatment-resistant' if they demonstrated less than 50% reduction in the PDSS score. Concerning patients already receiving adequate (⩾8 weeks in sufficient doses) SSRI therapy at intake, 'treatment-resistance' was defined as a CGI-I ⩾ 3 as judged by the study psychiatrist. Consequently, there is level 3 evidence that quetiapine-XR is not better than placebo as an augmentation therapy in PD patients with SSRI-resistance.

Risperidone. In an 8-week, flexible-dose, open-label study, 30 patients with chronic treatment-refractory anxiety disorders (PD, GAD, or social anxiety disorder) underwent augmentation therapy with risperidone (mean dose = 1.12 mg/day; SD = 0.68; range = 0.25–3.00). The PD subgroup (seven patients) demonstrated significant reductions in panic psychopathology (PDSS) and anxiety symptoms [Hamilton Anxiety Scale (HAM-A)], as well as a significant improvement in overall clinical state (CGI-S): risperidone was well tolerated, the most common side-effects being sedation/fatigue, appetite increase and weight gain and dizziness, the authors concluding that augmentation therapy with low-dose risperidone may alleviate chronic severe treatment-resistant PD.[114]

In a randomised, rater-blind, 8-week clinical trial, 56 patients suffering from PD (N = 43, 76.8% of the sample) or 'major depression with panic attacks', underwent augmentation of extant pharmacotherapy either with low-dose risperidone (mean = 0.53 mg; range = 0.125–1.0 mg) or paroxetine 30 mg.[115] All participants demonstrated significant reductions in the frequency and severity of panic attacks. The reductions were similar in the two groups, but augmentation with risperidone resulted in quicker clinical response. No significant side-effects were reported in either group. Up to 48% of patients dropped out of the study and the attrition rates in the two groups were similar. The initiation of risperidone was titrated, while paroxetine was initiated without titration. Another limitation – characteristic of all studies concerning antipsychotic administration in anxiety disorders – is that an 8-week follow-up period does not provide useful evidence on the long-term efficacy and safety of pharmacotherapy. Overall, there is level 3 evidence that risperidone may be an effective augmentation strategy for the treatment of non-responders to standard anti-panic pharmacotherapy.

Sulpiride and amisulpride. Sulpiride is an antagonist of D2/D3 receptors, with almost no affinity for other receptors.[116] In an open-label, 8-week study, sulpiride monotherapy (100, 150, or 200 mg/day, according to symptomatology) was administered in 19 treatment-resistant PD patients (mean age = 37.4 years).[14] During the week prior to sulpiride administration, previous pharmacotherapy (SSRIs) was washed out. At post-treatment, significant reductions were observed in the number of panic attacks (63.2% were panic-free), anxiety levels (HAM-A) and the overall clinical improvement (CGI-S). Noteworthy, among the more severely ill, more therapeutic gains were achieved with the lower dose of sulpiride (100 mg). The most common adverse effects included appetite change

(55%) and amenorrhea/galactorrhea (44%), both being mild in intensity. Sulpiride demonstrated a positive effect on the symptoms of treatment-resistant PD. In conclusion, there is level 3 evidence that sulpiride monotherapy may significantly reduce PD symptoms.

Previous data suggest that amisulpride may be an effective augmentation therapy in treatment-resistant mood disorders and somatoform disorders,[117–119] possibly because at low dosages (up to 10 mg/day) it selectively blocks presynaptic D2 and D3 autoreceptors, which leads to increased dopaminergic transmission in several cortical and limbic regions.[120] Although such mechanisms of action on the dopamine system might have anti-panic effects,[46] there is no report of amisulpride administration to treat panic psychopathology.

Administration of antipsychotics in patients with PD comorbid with a bipolar disorder

Patients with comorbid PD and bipolar disorder are usually not suitable for first-line treatments for PD –SSRIs and SNRIs – as monotherapy, due to the risks of rapid cycling and induced manic/hypomanic episodes.[121,122] Furthermore, it is important to distinguish between anxiety symptoms as part of the psychopathology of a bipolar disorder and the presence of a comorbid syndromal anxiety disorder. This distinction is clinically important as although SGAs may reduce anxiety symptoms in bipolar depression they may exacerbate symptoms in PD, possibly because of serotonergic antagonistic properties.[122] The following antipsychotics (in alphabetical order) have been used in patients with comorbid panic and bipolar disorders:

Quetiapine-XR. An 8-week, double-blind, placebo-controlled, randomised clinical trial in 149 patients with bipolar disorder comorbid with PD (N = 113) or GAD, compared the anxiolytic effects of quetiapine-XR 50–300 mg/day and divalproex-ER (500–3000 mg/day).[122] In all patients, and PD patients in particular, quetiapine-treatment (mean dose = 186 mg/day) produced rapid improvements compared with divalproex-treatment and placebo on both anxiety levels (HAM-A) and panic manifestations (Sheehan Panic Disorder Scale, SPS). When comparing the active treatments, quetiapine-XR was significantly superior to divalproex-ER. Both active medications were well tolerated, but weight gain was higher on quetiapine-XR. Thus, there is

level 2 evidence that quetiapine-XR may effectively reduce panic and anxiety manifestations in patients with comorbid PD and bipolar disorder.

Risperidone. An 8-week, double-blind, placebo-controlled, randomised clinical trial in 111 patients with bipolar disorder comorbid with PD (N = 80) or GAD, explored the anti-panic/anxiolytic effects of risperidone 0.5–4 mg/day.[123] Concerning all patients (i.e. irrespective of the comorbid anxiety disorder), risperidone was no more effective than placebo in reducing panic and anxiety symptomatology and in the overall clinical improvement. Remarkably, in the subgroup with comorbid PD, significantly greater reduction of anxiety symptoms (HAM-A) was seen in the placebo-group. Therefore, there is level 2 evidence that risperidone is not superior to placebo in alleviating panic and anxiety symptoms in patients with comorbid PD and bipolar disorder.

Ziprasidone. A randomised, double-blind, placebo-controlled parallel-group, 8-week trial explored the potential efficacy of ziprasidone monotherapy (mean dose = 146.7 mg/day; SD = 20.7 mg/day; range: 40–160 mg/day) in 49 bipolar patients with comorbid PD or GAD.[124] Ziprasidone monotherapy was not associated with a clinically significant improvement in patients' panic/anxiety psychopathology, while significantly more adverse effects (including abnormal movements) compared with placebo were evident. However patients were only moderately ill regarding their baseline panic/anxiety symptomatology. Consequently, there is level 2 evidence that ziprasidone monotherapy is not superior to placebo in alleviating panic and anxiety symptoms in patients with comorbid PD and bipolar disorder.

Administration of antipsychotics in patients with PD comorbid with schizophrenia or a related psychotic disorder

To the best of our knowledge, the effect that antipsychotic medications prescribed for schizophrenia or related psychoses have on comorbid panic and agoraphobic psychopathology has not been explored.

New-onset panic attacks as an adverse effect of the administration of an antipsychotic

We found three case-reports in which administration of an antipsychotic medication in a psychotic patient was associated with emergence of

new-onset panic psychopathology, which in two of the three cases remitted after switching to another antipsychotic.[125–127] These antipsychotic medications are as follows (in alphabetical order):

Clozapine. A 34-year-old woman developed multiple panic attacks and agoraphobia after a successful 20-week clozapine monotherapy (400 mg/day). The panic attacks improved modestly after dosage reduction to 250 mg/day. Full remission of the panic and agoraphobic psychopathology was only seen 2 months after the switch from clozapine to olanzapine 10 mg/day.[126]

Haloperidol. A 28-year old female with schizophrenia, while receiving haloperidol 6 mg/day developed recurrent panic attacks resistant to a 5-month alprazolam treatment.[127] A switch from haloperidol to risperidone 3 mg/day resulted in full remission of panic psychopathology, while psychosis did not deteriorate.

Olanzapine. A 36-year-old female schizophrenic patient, without history of panic psychopathology, significantly improved concerning her psychosis after switching to olanzapine 15 mg/day, but also demonstrated new-onset panic attacks 1 month later.[125] Olanzapine dosage was not reduced due to the marked improvement of her psychosis but panic attacks persisted for the next 6 months.

Clinical implications

The small-to-modest sample size, the lack of control groups and the open-label and short-term nature of most of the reviewed studies together hinder definitive conclusions regarding either the short-term and long-term efficacy of antipsychotic and anticonvulsant medications or their potential long-term side effects.

However, in selected treatment-resistant patients in which the clinician decides that administration of an anticonvulsant drug may result in clinical improvement, the following order of drug selection is suggested: (a) gabapentin (level 2); (b) any of the following drugs (level 3) based on the clinician's judgment regarding expected clinical gains *versus* adverse effects (alphabetically): carbamazepine, levetiracetam and valproate; (c) any of the following drugs (level 4) based on the clinician's judgment regarding expected clinical gains versus adverse effects (alphabetically): lamotrigine, oxcarbamazepine and vigabatrin. Clinicians must

be aware that tiagabine was not superior to placebo concerning reduction of PD psychopathology (level 3 evidence). Furthermore we stress that the use of valproate and carbamazepine, despite their potential effectiveness in PD, is limited in women of childbearing potential due to their possible teratogenicity and it has been suggested that these two anticonvulsant medications must be totally avoided during pregnancy.[128] European Medicines Agency (EMA) and Medicines and Healthcare Products Regulatory Agency (MHRA) guidance severely restrict the use of valproate in all women of childbearing potential.[129,130]

Similarly, in selected treatment-resistant cases in which the clinician decides that administration of an antipsychotic drug may result in clinical improvement, the following order of drug selection is suggested: any of the following drugs (level 3) based on the clinician's judgment regarding expected clinical gains *versus* adverse effects (alphabetically): aripiprazole (augmentation therapy), olanzapine (augmentation therapy), risperidone (augmentation therapy), sulpiride (monotherapy); clinicians must be aware that quetiapine-XR was not better than placebo as an augmentation therapy in PD patients with SSRI-resistance (level 3 evidence).

Finally, in patients with comorbid PD and bipolar disorder in which the clinician has to choose an antipsychotic that effectively reduces symptoms of both PD and bipolar disorder, with respect to the data available until now, which were reviewed in the present paper, quetiapine XR effectively reduces symptoms of both these psychiatric disorders when comorbid (level 2 evidence). Moreover, the clinician must be aware that both risperidone and ziprasidone are not superior to placebo in alleviating panic and anxiety symptoms in patients with comorbid PD and bipolar disorder (in both cases there is a level 3 evidence).

Conclusion

To summarise, previous studies suggest that a number of atypical antipsychotic and anticonvulsant medications may have a role in the pharmacotherapy of PD with or without psychiatric comorbidities, mainly as augmentation therapy in non-response to standard anti-panic treatment modalities. In patients with a primary diagnosis of PD, or without other comorbid psychiatric conditions, therapeutic gains were reported after treatment – mostly as augmentation therapy – with a

number of anticonvulsant drugs (carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, valproate, vigabatrin and tiagabine) and antipsychotic drugs (aripiprazole, olanzapine, quetiapine, risperidone and sulpiride, but not with quetiapine-XR). As regards tolerability and safety, reports suggest that atypical antipsychotics and anticonvulsants were generally well-tolerated in samples of PD patients. Moreover, bipolar patients receiving valproate or quetiapine-XR (but not risperidone or ziprasidone) demonstrated reductions of comorbid panic psychopathology. Finally, we traced a few case-reports of new-onset panic manifestations after the administration of some anticonvulsant (topiramate) or antipsychotic (clozapine, haloperidol, olanzapine) medications for other than PD psychiatric syndromes.

The main limitation of this review is that it is difficult to draw definite conclusions for everyday clinical practice as the great majority of existing studies follow an open-label methodology, and include small patient samples that lack control groups, which together may result in overestimation of benefit. Moreover, the small-to-modest sample size and the short-term nature of the vast majority of these studies prevents the drawing of definitive conclusions regarding the long-term efficacy and safety of antipsychotic and anticonvulsant medications and their potential long-term side effects, such as extra-pyramidal or metabolic adverse effects, sexual dysfunction and dermatological conditions. Furthermore, daily dosages of anticonvulsants and atypical antipsychotics that were administered in PD were low, which can be an additional reason for the lack of severe adverse events. Future studies in larger samples that address these limitations are needed. Comparison with first-line pharmacotherapies for PD may more precisely evaluate the efficacy of antipsychotics and anticonvulsants in treating panic psychopathology.

It has been hypothesised that specific PD patient subgroups might preferentially respond to the administration of anticonvulsants or antipsychotics. Thus, non-epileptic PD patients with an abnormal EEG or non-bipolar PD patients with 'mood instability' may represent groups for add-on anticonvulsant medication. Likewise, patients with rigid panic/agoraphobic cognitions and beliefs resistant both to CBT strategies and various standard pharmacological interventions might respond to augmentation with low doses of antipsychotic agents. However, further research is needed to enrich the few and often contradictory

extant data regarding the better response of such subgroups to antipsychotic or anticonvulsant pharmacotherapy. Finally, to the best of our knowledge, the effect that antipsychotic medications received for schizophrenia or related psychoses have on comorbid panic and agoraphobic psychopathology has not been explored.

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