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Pramipexole in unipolar and bipolar depression

AIMS AND METHOD

To review the evidence for this use of pramipexole in the treatment of unipolar and bipolar depression, a literature search on Embase and Medline was conducted in December 2003. The search was updated in July 2004. The reference sections of retrieved papers were searched for further relevant references.

RESULTS

There are limited data on the clinical use of pramipexole in affective disorders. Only two double-blind trials in bipolar depression and one in unipolar depression were retrieved. Most information is in the form of case reports and open studies. No dose-response relationships have been established and a wide range of doses has been employed in the reports.

CLINICAL IMPLICATIONS

In view of the fact that the evidence for the use of pramipexole is still limited at the time of writing, its routine clinical use cannot be recommended. The data appear promising, but further research is required to determine its role in affective disorders.

The monoamine hypothesis of depression has been the driving force behind antidepressant drug development for several decades. The theory holds that lower levels of serotonin, noradrenaline and dopamine may be involved in the pathophysiology of depression. The place of serotonin and noradrenaline in the clinical development of depression is well established. Most currently available antidepressants are thought to act via inhibition of the neuronal reuptake of either or both of these neurotransmitters.

More recently, an increased interest in the role of dopamine in the aetiology of depression has developed. This interest derives in part from the dopamine hypothesis of reward. In simple terms, pleasurable activity is associated with release of dopamine in the brain reward system (BRS). Conversely, inactivation of dopamine function can lead to anhedonia, the inability to experience pleasure, which is a core feature of depression. Furthermore, psychostimulants such as amphetamine and cocaine in low doses enhance dopamine release and cause activation and euphoria in normal volunteers. In higher doses or when taken repeatedly, they cause grandiosity, dysphoria and delusions. The withdrawal of these drugs frequently results in depression and anhedonia.

Data from animal studies and from limited human data indicate that dopamine agonists have antidepressant properties. The forced swimming test is one of the methods used to screen for antidepressant activity. When rats are forced to swim in a closed space from which they cannot escape, they will eventually stop attempting to escape and become immobile. Time to immobility in the swim test may be prolonged not only by antidepressants, but also by dopamine agonists. Furthermore, the anti-immobility effect of antidepressants in the forced swim test may be enhanced by co-administration of dopamine

agonists (Maj & Rogoz, 1999; Renard *et al*, 2001). In humans, the dopamine agonist bromocriptine has been shown to be as effective as imipramine in the treatment of depression (Willner, 1983). For a review of dopamine in depression, see Willner (1995) and Rampello *et al* (2000).

Only a limited number of antidepressants have potent activity on dopaminergic transmission. Of the antidepressants currently in use in the UK, the tricyclic antidepressants only have a very weak effect on dopamine reuptake, while venlafaxine and sertraline have more substantial, but still limited, dopaminergic effects, albeit at higher doses. Bupropion, amineptine and nomifensine are dopaminergic antidepressants that act partly via inhibition of dopamine reuptake. Bupropion is licensed in the UK only for smoking cessation. Amineptine has been withdrawn from major markets because of its propensity for addiction, while nomifensine, a selective dopamine reuptake inhibitor, was withdrawn due to the risk of acute haemolytic anaemia and intravascular hemolysis. There is no dopamine agonist currently licensed for the treatment of depression.

Pramipexole is a recently introduced dopamine D2/D3 agonist with preferential binding affinity to D3 receptors. It was licensed in the UK in 1998 at doses ranging from 0.375 to 4.5 mg per day for idiopathic Parkinson's disease.

We conducted a literature search in December 2003 on Medline (1966–2003) and Embase (1980–2003) using the terms 'pramipexole', 'dopamine agonists', 'bipolar disorder' and 'depression'. The search was updated in July 2004. The reference section of retrieved papers were hand-searched for further relevant references.

Results

Table 1, below, shows the details of papers retrieved from the literature searches.

Table 1. Papers retrieved in the literature search

Study	N	Study design	Patient characteristics	Dose of PPX	Duration of treatment	No PPX completers	Main adverse effects	Assessment of efficacy	Comments
Goldberg et al, 2004	Total 22 PPX 12 PLA 10	Double-blind, Placebo-controlled Adjunctive PPX or PLA to mood stabilisers	Refractory bipolar depression	1 to 2.5 mg target dose (up to 5 mg if needed)	6 weeks	10/12	Nausea, sedation, headache, 1 case of hypomania	PPX-67% PLA-20% (≥50% ↓ in HAM-D) PPX-60% PLA-9% (≥50% ↓ in MADRS)	Only 2 patients on PPX experienced remission in 6 weeks. Patients allocated to PPX and PLA may be dissimilar Flaws in the design and methodology
Zarate et al, 2004	Total 21 PPX 10 PLA 11	Double-blind, Placebo-controlled. Adjunctive PPX or PLA to lithium or valproate	Depression in Bipolar II	1–3 mg/day target dose (up to 4.5 mg max)	6 weeks	9/10	Insomnia, nausea, vomiting, tremor, agitation, somnolence	PPX-44% PRG-18.7% (≥50% ↓ in MADRS)	No evaluation of acute antidepressant effect. Patients in the PPX group had higher baseline MADRS scores
Rektorová et al, 2003	Total 41 PPX 22 PRG 19	Prospective, randomised trial comparing PPX and PRG. Adjunctive DA to L-dopa	Patients with mild to moderate depression and advanced PD	1.5 to 4.5 mg/day	8 months	19/22	Sleep disturbance, dyskinesias, nausea, orthostatic hypotension and hallucinations	PPX-44% PRG-18.7% (≥50% ↓ in MADRS)	Letter in Am J Psych. Tolerance to therapeutic effects noted, requiring dose increase
Ostow, 2002	22 patients	Open series. PPX alone or as adjunct to antidepressants or mood stabilisers	Mixed group of patients including, depressed, bipolar and borderline personality disorder	0.5 to 4.5 mg/day	<1 month to >6 months	N/A	Nausea, sedation, alertness	13 patients with marked improvements. No objective measures	
Lattanz et al, 2002	37 patients	Naturalistic, open label series. Adjunctive PPX to antidepressants and mood stabilisers	Refractory depression. 21 bipolar and 16 unipolar patients	0.375 to 1 mg/day	16 weeks	19/37	Dysphoria, psychomotor agitation, hypotension and tremor	68% response (21/31 pts with >50% ↓ in MADRS)	High drop out rate. Alterations in drug treatment and ECT during study. No difference between bipolar and unipolar
Perugi et al, 2001	18 patients, PPX 10 RPN 8	Open study, chart review of adjunctive PPX or RPN	Refractory bipolar II depression	0.75 mg to 1.5 mg/day (mean 1.23 mg)	4–34 weeks (mean 17.6 weeks)	17/18	GI disturbance, agitation, irritability, headache. 1 case of hypomania	Overall response rate 5/18 (27.8%) patients had transient response 44.4% PPX (4/10), RPN (4/8) 50%	Retrospective uncontrolled
Sporr et al, 2000	32 patients	Retrospective chart review. Adjunctive PPX treatment	Refractory depression. 12 patients with bipolar and 20 unipolar depression	0.125 to 2 mg/day (mean 0.7 mg)	24.4 weeks	20/32	Tremor, sedation, irritability. 1 case of hypomania	44% overall. 50% (6/12) bipolar, 40% (8/20) unipolar (Scale CGI-1)	
Corrigan et al, 2000	Total 174 PPX 104 FLU 35 PLA 35	Placebo run in, double-blind, placebo controlled study, comparing 3 fixed doses of PPX and fluoxetine with placebo	Depression excluding bipolar and refractory depression	0.375 mg, 1 mg, and 5 mg/day	8 weeks	65/104	Headache, nausea, somnolence, dizziness and insomnia	% response on ITT analysis. PPX: 0.375 mg –41.7%; 1 mg –37.1%; 5 mg –33.3%. Pla-25.7% Flu-48.6%	PPX 1 mg significantly superior to placebo at 8 weeks. Industry-sponsored study. Many missing data. Difficult to draw any firm conclusions.
Golberg et al, 1999, DeBattista et al, 2000	3 patients	Case reports. Adjunctive PPX	1 case of refractory depression, 2 cases of refractory bipolar depression	0.75 mg to 1.5 mg/day	6 weeks to 6 months	N/A	Nausea	3/3. Much improved	Improved sleep and restless legs in 1 patient
Szegedi et al, 1997	26 patients	Open label, monotherapy	Unipolar depression	1.75 mg to 6.25 mg/day	28 days	21/26	Agitation, nausea, insomnia, postural hypotension	CGI global-50% (13/26); HAM-D (6/26)	Only 23% achieved 50% reduction in HAM-D

PPX – Pramipexole; PRG – Pergolide; RPN – Ropinirole; FLU – Fluoxetine; PLA – Placebo; PD – Parkinson's disease; CGI – Clinical Global Impression; HAM-D – Hamilton's Depression Rating Scale; MADRS – Montgomery–Asberg Depression Rating Scale.



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Discussion

The majority of the data relating to the use of pramipexole in affective illness are in the form of chart reviews, naturalistic, open studies or case reports (Table 1). Only one double-blind controlled trial has been published in patients with unipolar depression (Corrigan *et al*, 2000). This trial compared three fixed doses of pramipexole with fluoxetine and placebo. Both pramipexole 1 mg and fluoxetine 20 mg showed significantly better improvement than placebo on the HAM-D scores at 8 weeks. More recently, there have been two double-blind, placebo-controlled trials of pramipexole as adjunct to mood stabilisers in bipolar depression (Goldberg *et al*, 2004; Zarate *et al*, 2004). These studies, although involving only small numbers ($n=43$ in total), demonstrated that the addition of pramipexole resulted in significant improvement in bipolar depression.

Rektorová *et al* (2003) compared pramipexole with pergolide, another dopamine agonist for the treatment of depression in patients with Parkinson's disease. Only pramipexole showed a significant effect on the objective measures of depression, using the Montgomery-Asberg Depression Rating Scale (MADRS), whereas both drugs significantly alleviated depressive symptoms using self-rating.

A significant proportion of the case reports and open studies involved patients with refractory depression, in which pramipexole was used as an adjunct to ongoing antidepressants and mood stabilisers. Response in this group was in the range of 40–50%. This indicates that there may be a role for pramipexole as an adjunctive treatment in refractory depression. It is also noteworthy that some reports document either tolerance developing to the antidepressant effects (Ostow, 2002) or having only transient effects (Perugi *et al*, 2001).

Although there is information on the potential use of pramipexole in both unipolar and bipolar depression, it is not known whether it is especially effective in any particular subtype. An earlier report with another dopamine agonist, bromocriptine, however, suggests that the antidepressant response may be greater in bipolar patients (Silverstone, 1984). This information may be useful in assessing the risk–benefit ratio in individual patients.

The optimal dose of pramipexole in depression is not yet established. Doses have varied from as low as 0.125 mg/day to as high as 9 mg/day. No clear dose–response relationship is established. In the study conducted by Corrigan *et al* (2000), patients on 5 mg/day had greater improvements compared with 1 mg/day, but this was limited by poor tolerability (mainly nausea) at the higher dose. Gradual dose escalation is thus required.

The adverse effects observed with pramipexole in these reports have been largely consistent with that of dopamine agonism. Common side-effects include nausea, sleep disturbance, agitation, postural hypotension, headaches and tremor. It has also been uncommonly associated with excessive daytime somnolence and sudden sleep onset episodes. As most data relating to adverse effects come from patients with Parkinson's disease, it is not clear if the rates at which CNS adverse effects (such as hallucinations, dyskinesia, insomnia, sleep attacks) occur will be any different than in patients with

depressive illness. At least four cases of hypomania have been reported with pramipexole (Sporr *et al*, 2000; Perugi *et al*, 2001; Goldberg *et al*, 2004; Zarate *et al*, 2004).

Conclusion

Data on the efficacy of pramipexole are still very limited. There is possibly a subgroup of patients who may respond preferentially to dopaminergic agents. At present, there is insufficient evidence to recommend the routine use of pramipexole. However, it may be considered as an alternative in patients with refractory unipolar and bipolar depression, in particular patients with marked motor retardation, hypersomnia, reduced sexual activity or melancholic features. It may also be considered as an option for the treatment of depression in patients with Parkinson's disease. There is no established dose and nausea is a dose-limiting adverse effect. The possibility of a manic switch, psychosis and other CNS manifestations should be borne in mind. Further studies are needed to establish the role of pramipexole in the treatment of unipolar and bipolar depression.

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