REVIEW ARTICLE

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Pirlindole in the Treatment of Depression and Fibromyalgia Syndrome

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Abstract

Depression and fibromyalgia syndrome are debilitating chronic conditions that impose a significant burden on individuals, families and society. Both depression and fibromyalgia have many overlapping symptoms, and antidepressants of several classes are among recommended treatment options for patients with fibromyalgia syndrome. Pirlindole is a selective and reversible inhibitor of monoamine oxidase (MAO) subtype A (MAO-A) that is approved in some European and non-European countries for the treatment of depression. The antidepressant efficacy and safety of pirlindole have been demonstrated in a number of placebo- and active comparator-controlled studies and are supported by many years of clinical experience in the treatment of depression. The drug's efficacy and safety have also been demonstrated, more recently, in the treatment of fibromyalgia syndrome. Pirlindole

has a favourable tolerability profile, with no deleterious effect on cardiovascular dynamics. The effect of pirlindole on sensorimotor performance relevant to driving a motor vehicle is similar to that of placebo, as pirlindole appears to have an activating rather than a sedating antidepressant profile. Because of its specific and reversible inhibition of MAO-A and relatively short elimination half-life, no tyramine or 'cheese' effect is likely after short- or long-term administration. The available evidence supports pirlindole as a safe and effective treatment option for the management of depression and fibromyalgia syndrome.

1. Introduction

Depression is a mood disorder characterized by persistent episodes of loss of interest or pleasure in ordinary activities, and experiences and feelings of helplessness, hopelessness and worthlessness, accompanied by additional symptoms such as changes in sleep, appetite or weight, and decreased energy, feelings of inadequacy, and difficulty concentrating or making decisions.[1] Fibromyalgia syndrome is a debilitating chronic medical condition that causes diffuse and/or specific pain throughout the soft tissues that support and move the bones and joints.[2] Associated somatic and psychological symptoms include fatigue, sleep disturbances, cognitive impairment, nervousness, depression and headaches.[2,3] Both depression and fibromyalgia syndrome are distressing and common disorders that impose a considerable burden on individuals, their families and society.[4-10]

Fibromyalgia syndrome and depression have many overlapping symptoms and often occur together.[2,3,11] In fibromyalgia syndrome, a psychic co-morbidity with variables such as anxiety and depression adversely affects the perception of disease severity, functional capacity, and the experience and tolerance of pain.[12] Furthermore, there is emerging evidence that similar candidate genes may be implicated in both fibromyalgia syndrome and depression, with polymorphisms of genes involved in the serotonergic, dopaminergic and catecholaminergic systems contributing to the aetiology of fibromyalgia syndrome.[13,14]

The selective and reversible inhibitor of monoamine oxidase (MAO) subtype A (MAO-A) [RIMA] pirlindole is approved in Portugal and other countries for the treatment of depression. This review summarizes the evidence for the efficacy and tolerability of pirlindole in the management of depression and fibromyalgia syndrome.

2. Literature Search Methodology

Articles included in the current review were all randomized, placebo- or active comparator-controlled trials or systematic reviews published in English between January 1970 and January 2011 and identified via a search of MEDLINE and EMBASE using the keywords ('pirlindole' OR 'pirlindol' OR 'pyrazidol') AND ('depression' OR 'depressive disorder' OR 'antidepressant' OR 'fibromyalgia' OR 'fibromyalgia syndrome'). This literature search was supplemented by AdisBase, a proprietary database of Wolters Kluwer Health/Adis. Additional references were identified from the reference lists of published articles and supplied on request from the reference files of Grupo Tecnimede, Sintra, Portugal. The inclusion of placebo-controlled trials in the current review may provide further insight into the efficacy of pirlindole not necessarily provided by analysis of trials comparing pirlindole with other active agents. In clinical trials of patients with psychiatric disorders, placebo response rates are often high, and vary considerably;[15,16] the average placebo response rate in trials of patients with depression has been estimated at 35–45%.[15] Consequently, placebo-controlled trials are important to demonstrate the efficacy of a drug,[16] as many trials of psychiatric disorders fail to confirm superiority of a drug over placebo.[15]

3. Burden of Disease and Current Pharmacological Treatment Options

3.1 Depression

Depression has been identified by the WHO as a leading cause of global burden of disease.[17] Worldwide, between 4% and 10% of the population is likely to experience major depression during their lifetime,[1] and population-based systematic reviews of the global burden of mental disorders estimate a median 1-year rate of major depressive disorder of 5.3%.[18] A recent survey-based study of general medical practices in six European countries (UK, Spain, Portugal, Slovenia, Estonia and the Netherlands) found a prevalence rate of major depressive disorder of 12.2% in consecutive practice attendees.[19] Depression was more than 60% more prevalent in women than in men, with the highest overall prevalence for women being observed in Spain, Portugal and the UK (18.4%, 17.8% and 13.2%, respectively).[19] The impact of major depression on functioning and quality of life (QOL) is illustrated in figure 1.

Choosing an effective treatment strategy for patients with depression is guided by the duration and severity of the condition.[1,21-23] A wide range of effective pharmacological treatment options is available for depression (summarized in table I). Although there are some suggestions of the superiority of one mechanism of antidepressant action over another, for the majority of patients the effectiveness of antidepressants is generally comparable between and within classes.[21,22] However, as the likely adverse events profiles of antidepressant medications differ, the selection of an antidepressant should take tolerability, safety and cost into consideration, as well as patient preference and the previous treatment response to a particular drug.[1,21,22] While newer classes of antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), noradrenergic reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors are considered first-line choices, the use of non-selective MAO inhibitors (MAOIs) has declined because of the necessity for dietary restrictions, adverse events related to their non-selective and irreversible binding profile, and the potential for drug-drug interactions.[1,21-23] The limitations of non-selective MAOIs, which irreversibly bind to both MAO-A and MAO-B isoenzymes, led to the development of RIMAs with improved tolerability and safety profiles; these include pirlindole and moclobemide. As MAO-A preferentially deaminates norepinephrine and serotonin, inhibition of MAO-A is recognized as a key factor for antidepressant effect.[28]

3.2 Fibromyalgia Syndrome

The recent European League Against Rheumatism (EULAR) multidisciplinary taskforce described fibromyalgia syndrome as a common rheumatological condition characterized by chronic widespread pain and reduced pain threshold, with hyperalgesia and allodynia.[2] The prevalence

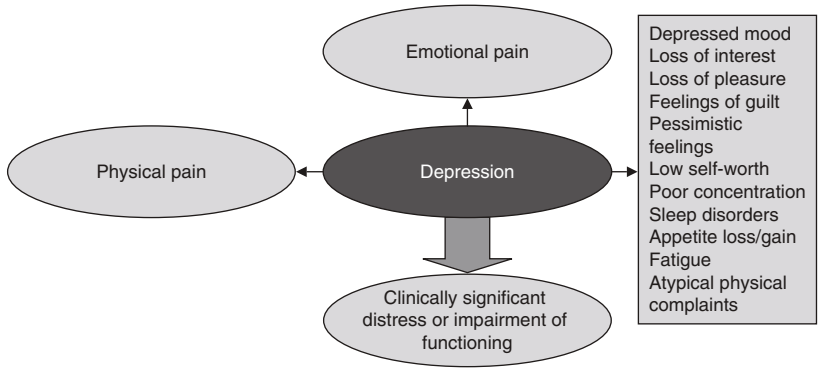

Fig. 1. Impact of major depression on functioning and quality of life including symptoms identified in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-Text Revision (TR) criteria for major depressive episodes.[20]

Table I. Antidepressants in the pharmacological management of depression and fibromyalgia syndrome[1,2,21-27]

Antidepressant class	Efficacy demonstrated in fibromyalgia syndrome
Tricyclic antidepressants	Amitriptyline
Tetracyclic antidepressants	No
Selective serotonin reuptake inhibitors	Fluoxetine, paroxetine, sertraline
Serotonin-norepinephrine reuptake inhibitors	Duloxetine, milnacipran, venlafaxine
Selective and non-selective MAO inhibitors	Selective (MAO subtype A): moclobemide, pirlindole
Norepinephrine-dopamine reuptake inhibitors	No
Noradrenergic and specific serotonergic antidepressants	No
Selective norepinephrine reuptake inhibitors	Reboxetine

MAO = monoamine oxidase.

of confirmed fibromyalgia syndrome in the general population in five European countries has been estimated as 3–5%, depending on the diagnostic criteria used, and as high as 14% in rheumatology outpatients.[29]

Fibromyalgia imposes a substantial socioeconomic burden on individuals and society, both in terms of the direct costs of healthcare resources and in terms of work loss and indirect costs to employers.[4,5,7-10] The condition can severely affect the QOL and functional status of individuals.[8,9] Patients with fibromyalgia syndrome have a considerably higher prevalence of co-morbidities than the general population, including dyslipidaemia, coronary heart disease, depression, migraine, irritable bowel syndrome and other gastrointestinal disorders.[4,5,7-10] The impact of fibromyalgia syndrome on functioning and QOL is illustrated in figure 2.

A number of antidepressants have also demonstrated efficacy in fibromyalgia syndrome (table I), with their use recommended in current evidence-based guidelines.[2,24] Other pharmacological treatment options for fibromyalgia include the antiepileptics gabapentin and pregabalin, opioid analgesics, NSAIDs, sedative-hypnotics, muscle relaxants, serotonin 5-HT_3 receptor antagonists (e.g. tropisetron) and dopamine D_3 receptor agonists (e.g. pramipexole).[2,24,25]

4. Pirlindole in the Treatment of Depression and Fibromyalgia Syndrome

Pirlindole has been used for the treatment of depression, an approved indication, for many years and has demonstrated some evidence of efficacy for the treatment of fibromyalgia syndrome, a non-approved indication.

Pirlindole (pyrazidol; 2,3,3a,4,5,6-hexahydro-8-methyl-1H-pyrazino-[3,2,1-jk]-carbazole HCl) is a tetracyclic chiral pyrazinocarbazole derivative with antidepressant properties.[30] Pirlindole combines in the same molecule structural features of MAO-A and those of imipramine (a tricyclic antidepressant). Dehydro-pirlindole is its principal metabolite.[31] The main mechanism of action of pirlindole and dehydro-pirlindole is selective, reversible and competitive inhibition of MAO-A;

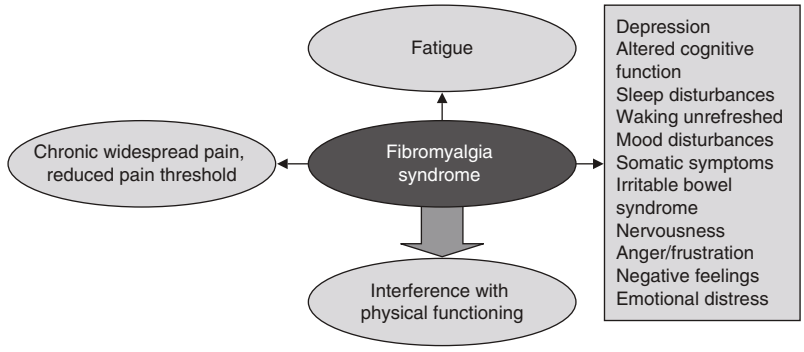

Fig. 2. Impact of fibromyalgia syndrome on functioning and quality of life including symptoms identified in the diagnostic criteria for fibromyalgia syndrome of the European League Against Rheumatism (EULAR) multidisciplinary taskforce[2] and the American College of Rheumatology.[3]

Table II. Single- and multiple-dose pharmacokinetic parameters of oral pirlindole in healthy male subjects[36] [a]

Pharmacokinetic parameter	Dose or regimen			
	75 mg (n = 8)	150 mg (n = 8)	225 mg (n = 8)	75 mg tid × 8 d (n = 9)[b]
C_{max} (ng/mL)	58 ± 44	206 ± 141	337 ± 161	42 ± 22
t_{max} (h)[c]	1.63 (1.00–2.00)	1.25 (0.83–2.00)	1.50 (0.83–2.00)	1.00 (1.00–2.50)
AUC_{∞} (ng • h/mL)	120 ± 111	471 ± 465	931 ± 697	NA
$t_{½}$ (h)	1.7 ± 0.5	2.1 ± 0.6	2.5 ± 1.1	5.2 ± 1.6
CL (L/h/kg)	13.7 ± 7.7	8.1 ± 6.2	5.0 ± 2.9	14.7. ± 7.8

a Data are presented as mean ± standard deviation unless stated otherwise.

b Data are for day 8.

c Median (range).

AUC_{∞} = area under the plasma concentration-time curve from time zero to infinity; **CL** = apparent total body clearance from plasma; **C_{max}** = maximum plasma concentration; **NA** = not available; **$t_{½}$** = elimination half-life; **tid** = three times daily; **t_{max}** = time to reach C_{max}.

the drug also possesses norepinephrine and serotonin reuptake inhibiting properties.[28,32,33] Although pirlindole itself is an inactive antagonist of γ-aminobutyric acid $(GABA)_A$ receptors *in vitro*, dehydro-pirlindole is a partial and selective $GABA_A$ receptor antagonist.[34,35] Silverstone[31] observed that the sensitivity of post-synaptic α_1- and α_2- adrenoceptors was increased without affecting receptor numbers after 3 weeks of continued administration of pirlindole in an animal study. Conversely, Bruhwyler et al.[28] reported that long-term administration of pirlindole increased the affinity of α_1- and β-adrenoceptors and α_2-adrenoceptor number in rat prefrontal cortex, as well as the number of α_1- and α_2-adrenoceptors and the affinity of β-adrenoceptors and 5-HT_2 receptors in the hippocampus.

4.1 Pharmacological Characteristics

4.1.1 Pharmacokinetics in Humans

The main pharmacokinetic parameters after single and repeated doses of pirlindole in healthy subjects are summarized in table II. Pirlindole is rapidly absorbed and distributed after oral administration, with appreciable amounts detectable in the brain, lung, liver, kidney and bone 30 minutes after drug administration.[36-38] After single-dose administration of 75–225 mg or repeated dosing of 225 mg/day in healthy male subjects, the maximum plasma concentration (C_{max}) was attained within 1.00–1.63 hours (table II).[36] Unchanged pirlindole was detectable in the plasma 15–30 minutes after single-dose administration. There was large interindividual variability in the plasma concentration-time curves, C_{max} and the area under the plasma concentration-time curve (AUC). Plasma concentrations declined in a mono-, bi- or tri-exponential pattern, according to the individual kinetics, with mean elimination half-life ($t_{½}$) values of 0.7, 1.7 and 4.9 hours for α, β and γ phases, respectively. The apparent total clearance was high (450–1000 L/h).[36] Taken together, these characteristics suggest an extensive first-pass effect. The relative bioavailability of pirlindole was >85%.

After repeated oral dosing (75 mg three times daily for 8 days), no accumulation was observed (table II).[36] Although renal excretion is the predominant route of elimination,[37] only 0.4–0.5% of the dose appeared in the urine as unchanged pirlindole after 24 hours.[36] The observed value of the mean renal clearance with repeated dosing (30–50 mL/min) is partly explained by the high affinity of pirlindole for plasma proteins (approximately 97% protein binding).

4.1.2 Pharmacodynamics in Humans

Short- and long-term administration of pirlindole did not alter platelet and plasma MAO-B activity, indicating a lack of inhibition of MAO-B.[39] However, long-term administration significantly reduced plasma norepinephrine concentrations and serotonin uptake and increased the expression of [^{3}H]-yohimbine binding sites.[39]

Pirlindole did not significantly differ from placebo in effect on sensorimotor performance relevant to driving a motor vehicle, and did not appear to potentiate the effects of alcohol (ethanol).[40] Nevertheless, consumption of alcohol should be avoided during treatment with pirlindole.[38]

Psychometric study of healthy subjects found that pirlindole improved concentration, cognitive function and complex reaction tasks while decreasing critical flicker fusion, with a peak pharmacodynamic effect observed between 4 and 6 hours after administration.[41] Computer spectral analysis of pharmaco-electroencephalogram (EEG) profiles suggested activating rather than sedating properties with long-term dosing of pirlindole.[41]

Short- and long-term administration of pirlindole in healthy subjects has not demonstrated a tyramine or 'cheese effect', a finding that is attributable to the drug's specific and reversible inhibition of MAO-A and short $t_{1/2}$.[42]

Long-term administration of pirlindole did not influence the secretion of hormones mediated by the hypothalamic-pituitary axis, including cortisol, triiodothyronine (T3), thyroxine (T4), gastrin, calcitonin, parathyroid hormone, testosterone, luteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone and prolactin.[43] However, a single high dose (300 mg) increased growth hormone levels, indicating that pirlindole influences norepinephrine metabolism in the CNS.

A single 225 mg dose of pirlindole had no effect on intraocular pressure or pupil diameter, suggesting that pirlindole does not have anticholinergic properties.[44]

4.2 Clinical Experience in Depression

4.2.1 Placebo-Controlled Studies

Double-blind, randomized, placebo-controlled studies have shown pirlindole to be significantly more effective than placebo in the treatment of depression, as measured by established evaluation criteria (table III).[52,53] In these studies, pirlindole produced significantly greater improvements in total Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale (HDRS) and Hamilton Anxiety Rating Scale (HARS) scores and individual subscale scores. The Brief Psychiatric Rating Scale (BPRS) was also assessed in one study in patients with a diagnosis of endogenous depression; only pirlindole (titrated to a dose of 300 mg/day) produced a significant decrease (not further defined) in BPRS total score, and in anxiety and depression, anergia and activation factor scores.[52] This study also demonstrated a marked improvement in Clinical Global Impression (CGI) score at day 35 in 60% of pirlindole recipients, compared with 27% of the placebo group.

In a multicentre study of inpatients with major unipolar depression with single or recurrent episodes, a total of 98 patients were randomized to receive pirlindole (n = 49) or placebo (n = 49).[53] Patients received pirlindole titrated to 300 mg/day over a 42-day treatment period. Fifty-nine patients completed the treatment period (30 placebo-treated and 29 pirlindole-treated patients) and there were significant improvements in MADRS, HDRS and HARS scores (all $p < 0.001$) in both groups from day 7 to day 42; these improvements were significantly greater with pirlindole than with placebo. When analysed using both intent-to-treat and per-protocol approaches, pirlindole produced a greater decrease than placebo in mean HDRS and HARS scores from day 28 to day 42 ($p < 0.05$ and $p < 0.01$, respectively) and in the mean MADRS score at day 42 ($p < 0.01$). At day 42, 72% of pirlindole recipients were classified as free of depression, compared with 21% of placebo recipients ($p < 0.001$). A total of 86% and 93% of pirlindole recipients responded to treatment, as measured by a greater than 50% decrease in HARS or MADRS scores, compared with 50% and 57%, respectively, in the placebo group (both $p < 0.01$).

4.2.2 Active Comparator-Controlled Studies

Pirlindole has been compared with other antidepressants in six short-term double-blind, controlled trials of up to 1 month's duration.[41,54,55,57-59] A total of 279 patients with diagnosed depression were treated in the studies. The active comparator was a tricyclic antidepressant in four trials (amitriptyline, desipramine or imipramine)[54-57] and a tetracyclic antidepressant in two trials (maprotiline or mianserin).[58,59] The most common

Table III. Description of the clinical trials included in the current review of adult patients with depression or fibromyalgia syndrome treated with pirlindole (PIRL)

Study	Comparator	Total no. pts	No. treated with PIRL	Mean/median age (y)	Female pts (%)	Duration of treatment (wk)	Dosage (mg/day)		Evaluation criteria	Main efficacy findings
							PIRL	comparator		
Treatment of depression										
Non-comparative										
Buchholz et al.[45]	BSL	18	18	44.0	56	5	225	NA	HDRS	+++
									BPRS	+++
									Zung	+++
Muldner and Wegehaupt[46]	BSL	17	17	44.0	0	8	225	NA	AMDP	+++
Muldner and Wegehaupt[46]	BSL	20	20	27.5	5	4–116	112.5–300	NA	Clinical evaluation	+++
Walcher[47]	BSL	42	42	NS	31	12–16	225–375	NA	HDRS	+++
									BDI	+++
Schwarz et al.[48]	BSL	20	20	61.5	0	4–27	100–300	NA	Clinical evaluation	++/+++
Schwarz et al.[49]	BSL	15	15	47.2	100	3	100–300	NA	HDRS	+++
									BDI	+++
Boissl and Rigler[50]	BSL	21	21	47.0	0	12–60	225–600	NA	Clinical evaluation	++/+++
Nahunek et al.[51]	BSL	63	63	49.0	59	3	75–600	NA	CGI	+++
PL-controlled (randomized, double-blind, parallel-group design)										
Zapletalek et al.[52]	PL	30	14	45.0	83	5	300	NA	BPRS	PIRL > PL
									HDRS	PIRL = PL
									HARS	PIRL = PL
									CGI	PIRL > PL
de Wilde et al.[53]	PL	98	49	48.0	65	6	300	NA	HDRS	PIRL > PL
									HARS	PIRL > PL
									MADRS	PIRL > PL
Active comparator-controlled (randomized, double-blind,[a] parallel-group design)										
Blaha[54]	AMIT	30	15	50.0	NS	3	225–450	150–300	LtD	PIRL > AMIT
									EDS, SVF	PIRL < AMIT[b]
									Bf-S	PIRL < AMIT[b]
Schapperle et al.[55]	IMIP	80	40	33.5	18	3	225	150	HDRS	PIRL = IMIP
									Immisch	PIRL = IMIP
									BDI	PIRL = IMIP

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Table III. Contd

Study	Comparator	Total no. pts	No. treated with PIRL	Mean/median age (y)	Female pts (%)	Duration of treatment (wk)	Dosage (mg/day)		Evaluation criteria	Main efficacy findings
							PIRL	comparator		
Schapperle et al.[55] c	AMIT	80	40	43.0	0	6	225	150	HDRS	PIRL = AMIT
									Immisch	PIRL = AMIT
									BDI	PIRL = AMIT
									Beltz	PIRL = AMIT
Schapperle et al.[55]	AMIT	80	40	41.0	50	6	225	150	HDRS	PIRL = AMIT
									Immisch	PIRL = AMIT
									BDI	PIRL = AMIT
									Beltz	PIRL = AMIT
Saletu et al.[56]	IMIP	50	25	38.9	56	3	225	150	HDRS	PIRL = IMIP[b]
									Zung, CGI	PIRL = IMIP
									Bf-S, MAS	PIRL = IMIP
									FPI	PIRL = IMIP
Lehmann et al.[57]	DES	39	19	NS	NS	3	225	50–150	HDRS	PIRL = DES
									AMDP	PIRL = DES
Poldinger[58]	MAPR	40	20	45.0	85	3	225	150	HDRS	PIRL = MAPR[b]
									SPA	PIRL = MAPR
de Wilde et al.[59]	MIAN	40	20	52.5	75	4	150–225	60–90	HDRS	PIRL = MIAN
									HARS	PIRL > MIAN
									BDI	PIRL > MIAN
									CGI	PIRL > MIAN
Tanghe et al.[60]	MOCL	111	52	47.0	65	6	150–300	300–600	HDRS	PIRL = MOCL
									HARS	PIRL = MOCL
									MADRS	PIRL = MOCL
Geerts et al.[61]	FLUOX	208	104	43.6	69.2	6	150–300	20	HDRS	PIRL = FLUOX
									HARS	PIRL = FLUOX
									MADRS	PIRL = FLUOX
Geerts et al.[61]	FLUOX	65	28	NS	NS	24	150–300	20	HDRS	PIRL = FLUOX
									HARS	PIRL = FLUOX
									MADRS	PIRL = FLUOX
Treatment of fibromyalgia syndrome										
PL-controlled (randomized, double-blind, parallel-group design)										
Ginsberg et al.[62]	PL BSL	100	33	39.7	88	4	75	NA	VAS pain	PIRL > PL
									Tender point score	PIRL > PL

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Table III. Contd

Study	Comparator	Total no. pts	No. treated with PIRL	Mean/median age (y)	Female pts (%)	Duration of treatment (wk)	Dosage (mg/day)		Evaluation criteria	Main efficacy findings
							PIRL	comparator		
									Global (investigator)	PIRL > PL
									Global (pt)	PIRL > PL
									SCL-90-R	PIRL > BSL
									Morning stiffness	PIRL > BSL
									Fatigue	PIRL > BSL
									Sleep disturbance	PIRL > BSL

a Unless stated otherwise.

b More rapid onset of action with PIRL compared with active comparator.

c Single-blind design.

AMDP = Arbeitsgemeinschaft fur Methodik und Dokumentation in der Psychiatrie (Association for Methodology and Documentation in Psychiatry); **AMIT** = amitriptyline; **BDI** = Beck Depression Inventory; **Beltz** = Beltz's Autoevaluation Scale; **Bf-S** = von Zerssen Mood Scale; **BPRS** = Brief Psychiatric Rating Scale; **BSL** = baseline; **CGI** = Clinical Global Impression; **DES** = desipramine; **EDS** = Erlangen Depression Scale; **FLUOX** = fluoxetine; **FPI** = Freiburger Personality Inventory; **HARS** = Hamilton Anxiety Rating Scale; **HDRS** = Hamilton Depression Rating Scale; **IMIP** = imipramine; **Immisch** = Immisch's Scale for Depression; **LtD** = performance test for endogenous depression; **MADRS** = Montgomery-Åsberg Depression Rating Scale; **MAPR** = maprotiline; **MAS** = Taylor Manifest Anxiety Rating Scale; **MIAN** = mianserin; **MOCL** = moclobemide; **NA** = not applicable; **NS** = not stated; **PL** = placebo; **pt** = patient; **SCL-90-R** = Symptom Checklist-90-Revised; **SPA** = Scale for General Psychopathological Findings; **SVF** = Scale of Vegetative Dysfunction; **VAS** = visual analogue scale; **Zung** = Zung Self-Rating Depression Scale. +++ indicates good improvement; ++ indicates moderate improvement.

pirlindole dose was 225 mg/day. In all except one trial, the antidepressant efficacy of pirlindole was considered at least equal to that of the active comparator. The exception was one trial in which patients reported in self-evaluation questionnaires that they felt slightly better with amitriptyline than with pirlindole.[54] In other efficacy evaluations in this study, pirlindole was more effective than amitriptyline in terms of the performance test in endogenous depression over the study period, whereas Erlangen Depression Scale, syndrome-specific scales and anxiety scale scores showed parallel courses.

In the comparison of pirlindole with mianserin,[59] both treatments produced significant ($p < 0.001$) improvements in HDRS, HARS and Beck Depression Inventory (BDI) self-evaluation scale scores from day 7 to day 28. There was no significant between-group difference in the evolution of the HDRS score; however, the evolution of the HARS and BDI scores individually, and the combined total score for HDRS plus HARS plus BDI, were significantly different in favour of pirlindole (each $p < 0.05$).

Pirlindole has been compared with amitriptyline, moclobemide and fluoxetine in four trials with study durations from 6 weeks up to 6 months.[55,60,61] Two of these trials, in which amitriptyline was the active comparator, were reported in the same publication.[55] A total of 160 inpatients with diagnosed depression were treated (80 with pirlindole and 80 with amitriptyline). Patients received pirlindole 225 mg/day or amitriptyline 150 mg/day for 6 weeks. No clinically relevant or statistically significant differences were observed between pirlindole and amitriptyline in HDRS, BDI, Immisch's Scale for Depression or Beltz's Autoevaluation Scale scores.

HDRS, HARS and MADRS were used to evaluate efficacy in 6-week trials of pirlindole versus the selective MAO-A inhibitor moclobemide[60] and the SSRI fluoxetine.[61] Pirlindole recipients received treatment at doses of 150, 225 or 300 mg/day. All active treatments produced significant improvements in the efficacy parameters, without significant differences in efficacy between pirlindole and moclobemide and fluoxetine. In the comparison with moclobemide, 80%

of patients in the pirlindole group and 67% of patients in the moclobemide group had a response defined as superior or equal to 50% improvement in the HDRS score at 6 weeks ($p > 0.05$).[60] Sixty-five patients in the study comparing pirlindole with fluoxetine entered an extension phase and were treated for a total of 6 months.[61] The therapeutic equivalence of pirlindole and fluoxetine was confirmed, with no significant differences in efficacy evaluations.

A summary of the descriptions and main efficacy findings of these studies is presented in table III.

A recently published meta-analysis of nine randomized controlled trials evaluated the efficacy and tolerability of pirlindole compared with other active antidepressant agents in patients with depression.[63] The results showed that pirlindole was significantly better at reducing anxiety symptoms than its comparators.[63]

4.2.3 Non-Comparative Studies

In an open-label, dose-finding study in 15 depressed female patients, the antidepressant efficacy of pirlindole (measured by HDRS and BDI) was apparent within 2–5 days in 73% of patients, with doses ranging from 100 to 300 mg/day (150 mg/day in the majority of patients).[48] A very good, moderate or mild improvement in depression was observed in 73% of 257 patients enrolled as inpatients and/or outpatients in other uncontrolled, open-label trials reviewed by Bruhwyler et al.[39] Higher age did not reduce the therapeutic efficacy or tolerability of pirlindole,[51] and uniform, gradual and prolonged improvements in all subscores of the HDRS were observed during treatment, without the increase in agitation subscores often observed with non-selective MAOIs.[45]

Finally, 1330 patients received pirlindole 150–500 mg/day for up to 32 months in a post-marketing study reviewed by Bruhwyler et al.[39] Antidepressant efficacy, as measured by a range of rating scales, including HDRS, was considered very good or moderate in 61%, and mild in 10%. Depression was rated as unchanged or deteriorated in 29%.

A summary of the descriptions and main efficacy findings of these studies is presented in table III.

4.3 Clinical Experience in Fibromyalgia Syndrome

Pirlindole is specifically recommended for the treatment of fibromyalgia syndrome in the current evidence-based EULAR guidelines, which reviewed the evidence for the effectiveness of antidepressants in fibromyalgia syndrome and found pirlindole was effective in reducing pain.[2] The recommendation for pirlindole is, however, based on the results of a single high-quality trial in 100 patients treated with pirlindole that demonstrated significant improvements in pain outcomes compared with placebo.[62] It should also be noted that functional status was not assessed in this study.

In this study by Ginsberg et al.,[62] 100 patients with primary fibromyalgia syndrome according to the then-current American College of Rheumatology (ACR) classification[64] were randomized to treatment with pirlindole 75 mg twice daily or identical placebo for 4 weeks. No other medications for fibromyalgia syndrome were permitted, except paracetamol (acetaminophen) if needed for severe pain. The inclusion criteria included adult patients aged between 18 and 75 years with a history of widespread pain for at least 3 months and with pain on digital palpation present in at least 11 of the 18 classical tender point sites. Efficacy assessments included pain evaluation by means of a visual analogue scale (VAS), morning stiffness duration, tender point score, a psychological evaluation using the Symptom Checklist-90-Revised (SCL-90-R) self-report inventory,[65] and global evaluation by patients and the investigator.

Pirlindole significantly improved all efficacy parameters from baseline ($p < 0.05$), while only tender point score, psychological score and global evaluation by patient improved with placebo ($p < 0.05$).[62] At the end of the study, pirlindole was significantly superior to placebo for VAS pain score, tender point score, and global evaluation by patients and the investigator ($p < 0.05$). Pirlindole also significantly improved fatigue and sleep disturbances ($p < 0.05$). Pirlindole was well tolerated (see section 4.4).

A number of meta-analyses of the effectiveness of antidepressants in fibromyalgia syndrome have

included the Ginsberg et al.[62] study of pirlindole.[25-27] These analyses have found pirlindole to be effective in reducing pain,[25-27] regardless of setting (primary care vs specialized care).[25]

4.4 Safety and Tolerability

Pirlindole has been shown to be well tolerated during both short-term (≤6 weeks) and medium-term (≤6 months) use.[61] An overview of the most common treatment-emergent adverse events in patients with depression or fibromyalgia syndrome treated with pirlindole in placebo- and active comparator-controlled clinical trials in which safety data were reported, and in a large open-label post-marketing study in 1330 patients, is presented in table IV. The most commonly reported adverse events with pirlindole were gastrointestinal symptoms (including nausea and vomiting, diarrhoea, constipation and gastric discomfort), headache, agitation, insomnia and dry mouth. The majority of adverse events were of mild-to-moderate severity. The relationship of the study drug to adverse events was generally not reported, but in the double-blind study by de Wilde et al.,[53] adverse events were considered related to study medication in 53% of cases in the placebo group and in 38% of cases in the pirlindole

Table IV. Summary of the most common treatment-emergent adverse events reported in patients with depression or fibromyalgia syndrome treated with pirlindole in representative placebo-controlled[53,62] or randomized, double-blind, parallel-group, active comparator-controlled[40,55,58-61] studies and in a pivotal open-label study[39] [a,b]

Adverse event	Placebo or active comparator-controlled trials						Open-label trial[c]
	pirlindole (n = 380)	placebo (n = 93)	amitriptyline (n = 55)	maprotiline[d] (n = 20)	moclobemide (n = 59)	fluoxetine[e] (n = 102)	pirlindole (n = 1330)
Gastrointestinal symptoms	58 (15.3)	14 (15.1)	0	?	19 (32.2)	18 (17.6)	10 (0.7)
Dry mouth	21 (5.5)	5 (5.4)	5 (9.1)	16 (80.0)	11 (18.6)	4 (3.9)	62 (4.7)
Agitation	22 (5.8)	3 (3.2)	0	?	16 (27.1)	?	0
Headache	28 (7.4)	5 (5.4)	0	?	10 (16.9)	8 (7.8)	6 (0.5)
Insomnia	20 (5.3)	1 (1.1)	0	?	10 (16.9)	4 (3.9)	0
Drowsiness	10 (2.6)	3 (3.2)	0	?	10 (16.9)	4 (3.9)	38 (2.9)
Tremor	6 (1.6)	2 (2.2)	4 (7.3)	?	3 (5.1)	?	2 (0.2)
Dizziness/vertigo	14 (3.7)	4 (4.3)	0	?	7 (11.9)	4 (3.9)	13 (1.0)
Cardiovascular disturbances	7 (1.8)	4 (4.3)	1 (1.8)	?	13 (22.0)	?	18 (1.4)
Accommodation disturbances	3 (0.8)	2 (2.2)	3 (5.5)	4 (20.0)	1 (1.7)	?	0
Sweating	3 (0.8)	0	1 (1.8)	?	8 (13.6)	?	2 (0.2)
Skin symptoms	3 (0.8)	0	0	?	0	?	0
Concentration difficulties	2 (0.5)	0	0	?	3 (5.1)	?	0
Confusion	1 (0.3)	2 (2.2)	0	?	3 (5.1)	?	0
Anorexia	1 (0.3)	2 (2.2)	0	?	0	?	0
Weakness	0	0	0	?	0	?	52 (3.9)
Other	117 (30.8)	13 (14.0)	0	?	0	?	55 (4.1)

a Data are presented as no. (%) of patients.

b In the study by Schapperle et al.,[55] a double-blind comparison of pirlindole vs imipramine, no significant adverse events were observed in either group. In the study by de Wilde et al.[59] a double-blind comparison of pirlindole vs mianserin, 1/20 patients in the mianserin group (5%) had an adverse event (dry mouth). Adverse events for pirlindole (insomnia in 1/20 patients [5%]) are included in the table.

c Data reviewed in Bruhwyler et al.[39] from data published in German.

d In the Poldinger[58] study, only the most frequent adverse events were reported; the incidence of other less common adverse events is unclear.

e In the Geerts et al.[61] study, only the most frequent adverse events were reported; the incidence of other less common adverse events is unclear.

? indicates incidence unclear.

group. In general, pirlindole had a tolerability profile similar to or better than other active comparators and placebo.

No serious adverse events were reported, and no adverse events related to the 'tyramine effect' ('cheese effect') were reported. In a study of pirlindole in patients with a diet high in tyramine-rich foods, there were no effects on blood circulation, blood pressure or pulse rate, and no sign of interactions with concomitant medications, including tranquillizers, antipsychotics, antiepileptics and neurotropics.[49]

Pirlindole was associated with a very low incidence (0.8% in the comparative studies) of disturbances in accommodation difficulties, an indication that it does not possess anticholinergic properties, as mentioned in section 4.1.2. Consequently, unlike tricyclic antidepressants such as amitriptyline, pirlindole is not contraindicated in patients with glaucoma or prostatic hypertrophy.[66,67]

Pirlindole is not associated with clinically significant alterations in cardiovascular parameters, and does not adversely affect haematological and biochemical variables.[38,57] Furthermore, pirlindole does not appear to alter sleep parameters.[68] However, in patients experiencing insomnia when treated with pirlindole, the last dose should be administered 5–6 hours before bedtime.[38]

As depression and certain other psychiatric disorders are themselves associated with an increased risk of suicide, patients who are started on antidepressant therapy, regardless of the history or thoughts and/or behaviours associated with suicide, should be monitored for depression-related suicidal ideation, suicidal thoughts and self-harm (or any other psychological changes) during the first weeks of treatment until significant improvement in symptoms occurs.[38]

The frequency of epileptic seizures should be monitored in patients with epilepsy, as high doses of pirlindole induced seizures in a rodent study.[38] However, no reports of seizures have been identified in clinical studies or post-marketing data.[38]

Data on the use of pirlindole in pregnancy and lactation are limited and administration of pirlindole is not recommended in these situations.[38] Pirlindole is also not recommended for the treatment of children aged <12 years.

Administration of pirlindole is contraindicated in patients with serious haematological, hepatic or renal disorders.[38] Concomitant medication should be monitored in patients treated with pirlindole who are suffering from severe cardiovascular disorders, such as conduction disturbances, angina pectoris or recent myocardial infarction.

4.4.1 Drug Interactions

Administering pirlindole in combination with tricyclic antidepressants may not increase the incidence of adverse events compared with monotherapy.[38] However, when the co-administration of pirlindole and a tricyclic antidepressant is clinically recommended, the two drugs should be initiated simultaneously, starting with lower doses than usual; where pirlindole is being replaced by a tricyclic antidepressant, a washout period of 7 days should be used.[38]

Pirlindole should not be used concurrently with non-selective MAOIs or sympathomimetic amines (dopamine, metaraminol, epinephrine, norepinephrine or isoproterenol) because of an increased risk of hypertension.[38] An interval of 14 days is recommended between the administration of a non-selective MAOI and pirlindole. Concomitant administration of pirlindole with antihypertensives (methyldopa, reserpine and guanethidine) may potentiate their effect and is not recommended.[38]

5. Conclusions

Clinical experience over many years in the treatment of depression has established the efficacy and favourable tolerability of pirlindole. Although it is noted that most published studies enrolled a relatively small number of patients and very recent studies are lacking, a number of double-blind placebo-[52,53] or active comparator-controlled[54-61] trials have demonstrated the antidepressant efficacy of pirlindole, and its efficacy has also been demonstrated in the treatment of fibromyalgia syndrome.[62]

Placebo- and active comparator-controlled trials have shown pirlindole to have a favourable tolerability profile, with only headache, sleep disturbances and agitation occurring at a substantially

higher (though still low) rate than placebo. The lack of deleterious effects on cardiovascular dynamics, inotropy and electrophysiology suggests that pirlindole may be beneficial in patients with depression with a previous history of cardiovascular disorders,[69] the lack of a relevant tyramine interaction provides an advantage over non-selective MAOIs, and pirlindole does not possess anticholinergic properties. Pirlindole, or its metabolite dehydro-pirlindole, also appears to possess antidepressant properties independent of MAO-A inhibition, including activity as a partial and selective $GABA_A$ receptor inhibitor.[34,35]

An interesting and less well known use of pirlindole is in the treatment of patients with fibromyalgia syndrome. Antidepressants from a number of classes have shown efficacy in fibromyalgia syndrome and are recommended in current treatment guidelines among options for the management of fibromyalgia.[2,24] The role of pirlindole in fibromyalgia syndrome is supported by a well designed trial that showed that pirlindole significantly improved pain and efficacy outcomes compared with placebo.[62] Specifically, at the end of the study, pirlindole 150 mg/day was significantly superior to placebo for all pain parameters, tender point score, and global evaluation by patients and the investigator, and improved fatigue and sleep disturbances. As has been established in depression, pirlindole was well tolerated by patients with fibromyalgia syndrome.

The inclusion of placebo-controlled trials in the current review may provide further insight into the efficacy of pirlindole. On the basis of the best available evidence, pirlindole has a useful role to play in the treatment of depression and fibromyalgia syndrome.

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