ORIGINAL RESEARCH ARTICLE

Clin Drug Investig 2011; 31 (1): 61-71
1173-2563/11/0001-0061/$49.95/0

Pirlindole in the Treatment of Depression
A Meta-Analysis

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Abstract

Background: Depressive disorders are common health problems. Both preclinical and clinical studies have shown that pirlindole, a tetracyclic compound, is suitable for the management of depression; however, a systematic review is needed to accurately select randomized controlled trials (RCTs) for a meta-analysis that will provide more consistent and accurate results regarding the efficacy and tolerability of the drug.

Objectives: To evaluate the efficacy and frequency of adverse events with pirlindole in comparison with active comparators (monoamine oxidase inhibitors [MAOIs], tricyclic antidepressants, tetracyclic antidepressants, and selective serotonin reuptake inhibitors [SSRIs]) for the treatment of major depression.

Methods: Data were searched through MEDLINE (via PubMed), EMBASE, the Cochrane Central Register of Controlled Trials and a manual search through the sponsor's available archives (1966 to 30 August 2010). The meta-analysis was performed using the Mantel-Haenszel technique and analysing data through Comprehensive Meta-Analysis software version 1.0.23. Studies were included if they were RCTs evaluating the efficacy and number of reported adverse events with pirlindole in comparison with active comparators for the treatment of major depression in adults. Placebo-controlled trials were excluded to minimize study heterogeneity.

Results: This systematic review included ten published articles and one non-published report corresponding to a total of 13 clinical trials in the adult population. Two RCTs were excluded from the meta-analysis because the comparator was placebo. Two more studies were excluded, one because randomization could not be confirmed and the other because it described follow-up data on patients from a study that had already been included in the meta-analysis. Therefore, only nine RCTs were included in the meta-analysis. No differences were found between pirlindole and its active comparators with regard to the percentage of patients whose clinical condition improved by 50% according to the Hamilton Depression Rating Scale (HDRS) [odds ratio (OR) 1.52; 95% confidence interval [CI] 0.92, 2.51; p = 0.11] and Hamilton Anxiety Rating Scale (HARS) [OR 1.15; 95% CI 0.69, 1.90; p = 0.59]. With

regard to the improvements in HDRS and HARS, the results were favourable for patients treated with pirlindole (depression: absolute value 0.18; 95% CI −0.01, 0.37; p = 0.06; anxiety: absolute value 0.26; 95% CI 0.03, 0.48; p = 0.03).

Conclusion: This systematic review and meta-analysis showed that all RCTs included reported efficacy outcomes for pirlindole comparable to those of its comparators, and that pirlindole was significantly better in terms of reducing anxiety symptoms. However, the analysis of these results should take into account the quality of the original included articles, which had a mean Jadad trial quality score of 3.7 (out of 5). Therefore, further clinical trials should be conducted to evaluate the benefits of pirlindole.

Introduction

Depressive disorders are common mental health problems affecting around 121 million people worldwide.[1] According to the WHO, depression is a leading cause of death and disability in both developing and industrialized countries and was the fourth leading contributor to the global burden of disease in 2000. It represents a significant public health problem, affecting people of all ages, backgrounds and sexes,[1] but is more common in women.[2]

When depression is correctly diagnosed, and appropriately and consistently treated, it has a good prognosis. Currently a wide variety of effective treatment options are available for depression.[3] Antidepressant medications and brief, structured forms of psychotherapy are effective for 60–80% of those affected.[3] Currently there are a considerable number of heterocyclic drugs, such as selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and newer classes of antidepressants such as noradrenergic reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors (SNRIs). Therefore it is not always easy to know which drug works best taking into account their efficacy and tolerability profiles, associated costs and patient characteristics.[4,5]

Among the first drugs used to treat major depressive disorders were the MAOIs, an important group of antidepressants with documented efficacy, particularly for patients with treatment-resistant, bipolar and atypical depressive syndromes.[6,7] MAOIs act by increasing brain levels of the mood-elevating neurotransmitters serotonin, norepinephrine and dopamine, thereby counteracting their catabolism.[8] Their mechanism of action is based on monoamine oxidase (MAO) inhibition with consequent reductions in serotonin, norepinephrine and, to a lesser extent, dopamine levels.[9] While inconsistently prescribed by physicians, MAOIs have been claimed to have special value in some psychiatric syndromes, including reactive, neurotic or atypical depressive conditions, depressive-anxiety states and phobic anxiety-depersonalization syndromes.[6,9] As a consequence, MAOIs are indicated for the treatment of anxiety disorders, such as social phobia, panic disorder, post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder.[6,9]

Despite their documented efficacy in the treatment of major depression, the use of MAOIs has been declining in recent years because of their adverse effects, which include severe hypertensive events attributable to their non-selective and irreversible binding profile.[6,8] These drugs are defined as non-selective, as they generally bind to both MAO-A and MAO-B isoenzymes. MAO-A and MAO-B are two different isoforms of MAO with different roles in the treatment of depression.[6,10] Furthermore, the persistent and irreversible binding of the drug to the MAO enzyme is responsible for permanent destruction of enzyme function, meaning renewed activity is possible only after new enzymes have been synthesized.[11] These factors account for the dangerous

association of MAOIs with insignificant concentrations of vasopressors.[6,7] Usually, the isoenzyme MAO-A is able to destroy norepinephrine when it starts to accumulate.[7,10] However, when large amounts of tyramine are ingested in the regular diet while MAOIs are being taken, patients can develop a hypertensive crisis as a result of a lack of MAO-A activity.[7]

The increasing need for the development of new medications with superior tolerability and safety profiles led to the development of numerous second-generation drugs, including the selective and reversible MAOIs.[12] More specifically, these developments led to the recognition of the importance of reversible inhibitors of MAO-A that combine antidepressant activity with a reduced risk of hypertensive crisis because they competitively and selectively inhibit MAO-A.[12,13] As the isoenzyme MAO-A is more specific for metabolizing the monoamines that are more closely related to depression, such as serotonin and norepinephrine, an antidepressant must inhibit this form of MAO. Therefore, when high levels of tyramine have been ingested, the subsequent release of norepinephrine will free the MAO-A enzyme from the reversible inhibitor, restoring its activity and allowing the destruction of dangerous amines.[14]

Pirlindole hydrochloride (2,3,3a,4,5,6-hexahydro-8-methyl-1H-pyrazino [3,2,1-jk]-carbazole HCl) is a tetracyclic compound that was synthesized in the late 1960s. Its main mechanism of action is the selective and reversible inhibition of MAO-A; an inhibitory effect on norepinephrine and serotonin reuptake has also been described.[15] This compound has been characterized as a potential antidepressant drug in preclinical studies.[16] When compared with tricyclic antidepressants and non-selective MAOIs, pirlindole was found to have a better safety profile because of a lower interaction with the cardiovascular system and a lack of a pressor effect after tyramine and norepinephrine exposure.[15]

Comparative clinical studies conducted to evaluate efficacy and tolerability revealed that pirlindole has a favourable pharmacological and therapeutic profile.[16-18] It has also been shown that pirlindole has a combined action on two of the biochemical factors (inhibition of MAO-A and reuptake of serotonin and norepinephrine) thought to be involved in the pathogenesis of depression, and that it does not affect cardiovascular parameters or measured haematological and biochemical variables.[19,20]

Pirlindole has been used for the treatment of depression for many years, and has been marketed in Portugal in 50 mg tablets. Although both preclinical and clinical published studies have shown that pirlindole has pharmacological, pharmacokinetic and toxicological properties that make it suitable for the management of depression, analysis of all the available RCTs will provide a consistent, comprehensive and more accurate estimate of its efficacy and general tolerability. In conducting this systematic review and meta-analysis we aimed to expand the available data on the efficacy and frequency of adverse events of pirlindole for the treatment of adults with major depression in order to increase knowledge of the benefits of treatment with pirlindole.

Methods

Data Sources and Study Selection Criteria

This review was carried out through a systematic literature search of MEDLINE (via PubMed), EMBASE and the Cochrane Central Register of Controlled Trials. The literature search was performed (1966 to 30 August 2010) in order to evaluate the efficacy and adverse events profile of pirlindole in the treatment of major depression, in accordance with the following strategy:
(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR (clinic* [tw] AND trial* [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (latin [tw] AND square [tw]) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR

prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT animal [mh] AND (pirlindol* OR 'carbazol hydrochloride' OR implementor*)

Thirty-nine references were identified through this systematic literature search. One more reference, corresponding to a non-published report, was identified through a manual search of the sponsor's available archives for RCTs of pirlindole in the treatment of depression. In total, 40 references were identified. Abstracts of conference proceedings were excluded from this systematic literature search. Articles written in a language other than English, such as Russian, were reviewed by a professional translator.

The studies selected for systematic review were examined and were considered eligible if they were RCTs that evaluated the efficacy and adverse events profile of pirlindole in comparison with placebo or other active drugs for the treatment of major depression or depressive episodes in patients with bipolar disease in adults (table I). No restrictions were set in terms of the studies' year of publication.

Data Extraction

All the included RCTs were independently reviewed by two investigators (disagreements were resolved through discussion and achievement of consensus between reviewers) and their quality was assessed by application of the Jadad scale,[28] which evaluates study randomization (0 = not randomized; 1 = randomized, not described; 2 = randomized and described), blinding (0 = open label; 1 = single blind; 2 = double blind), and the reporting of withdrawals and dropouts (0 = not described; 1 = described).

After careful analysis of the selected articles the following data were extracted: publication data (when applicable), therapeutic indication, pirlindole dose, comparator, comparator dose, randomization, blinding, study design, diagnostic criteria, dropouts, percentage of female patients, mean age of patients, efficacy scales that were used and their mean values (clinical efficacy measures), percentage of patients whose clinical condition improved by 50% on the Hamilton Depression Rating Scale (HDRS) and Hamilton Anxiety Rating Scale (HARS), and number of patients with adverse events. No additional data were evaluated.

For the majority of the selected RCTs, the patients enrolled were inpatients with major depression. Patients were followed for different treatment periods, as follows: 21 days in five RCTs,[17,20,22-24] 42 days in four,[17,18,25,26] 28 days in two,[16,21] and 35 days[27] and 180 days[26] in one RCT each.

With regard to the primary endpoints, the HDRS and/or HARS were used in the majority

Table I. Evaluation and characterization of clinical trials included in the systematic review

Study	Year	Jadad score	Inclusion in the meta-analysis	Randomization	Pirlindole dose (mg)	Comparator	Comparator dose (mg)
Lehmann et al.[20]	1983	3	Yes	Yes	225	Desipramine	150
Renfordt[21]	1983	2	No	Unknown	300	Amitriptyline	200
Blaha[22]	1983	3	Yes	Yes	225–450	Amitriptyline	150–300
Schäpperle et al.[17]	1983	3	Yes	Yes	225	Amitriptyline	150
Schäpperle et al.[17]	1983	3	Yes	Yes	225	Imipramine	150
Saletu et al.[23]	1983	3	Yes	Yes	225	Imipramine	150
Pöldinger[24]	1983	4	Yes	Yes	225	Maprotiline	150
Tanghe et al.[18]	1997	5	Yes	Yes	150–300	Moclobemide	360–600
De Wilde et al.[25]	1996	4	No	Yes	300	Placebo	
De Wilde et al.[16]	1997	4	Yes	Yes	150–225	Mianserin	60–90
Geerts et al.[26]	1999	5	Yes	Yes	150–225	Fluoxetine	20
Geerts et al.[26]a	1999	5	No	Yes	150–225	Fluoxetine	20
Zapletálek et al.[27]	1981	4	No	Yes	300	Placebo	

a Follow-up of subgroup of patients included in the study above.

of the selected RCTs. The other endpoints were: clinical criteria; Beck Depression Inventory (BDI); Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised (DSM-III-R); Leistungstest für Depression (LTD); Montgomery-Åsberg Depression Rating Scale (MADRS); Clinical Global Impression (CGI); Brief Psychiatric Rating Scale (BPRS); Vinar's Complemented Scale of Side Effects (DVP); Scale for General Psychological Findings; Zung Self-Rating Scale; Immich scores; and Erlangen scale. However, in this meta-analysis, only HDRS and HARS scores were evaluated. Endpoint evaluations were mainly performed before initiating the treatment, at the end of the treatment period and every week between these two dates (before and at the end of the treatment). Patients' inclusion criteria, the number of dropouts and the reasons for dropping out are described in table II. The proportion of dropouts ranged from 5% to 40% in the total sample (i.e. all patients included in the RCTs selected for the systematic review). In the pirlindole group, the proportion of dropouts ranged from 10% to 40%, compared with 0% to 39% in the active comparator group. The data set used (intent to treat [ITT] or per protocol [PP]) was described only in the study by Geerts et al.,[26] and the meta-analysis was therefore performed assuming that all of the results obtained were derived from ITT data sets.

Meta-Analysis

The global assessment of efficacy parameters and number of reported adverse events was carried out through a meta-analysis that allowed an overall analysis of each study's results in a group evaluation. Odds ratios (ORs) and absolute values for evaluated parameters were calculated.

Meta-analysis was computed using the Mantel-Haenszel technique. Methods of fixed effect meta-analysis are based on the mathematical assumption that a single common (or 'fixed') effect underlies every study in the meta-analysis. According to this assumption, if every study were infinitely large, it would yield an identical result. This is the same as assuming there is no (statistical) heterogeneity among the studies.[29]

One of the main parameters that can limit the use of meta-analysis techniques is the lack of homogeneity in the information presented in the articles. Therefore, the scales that were used were taken into account when performing the evaluation. The Q-test for heterogeneity was used to determine the homogeneity of the studies. The difference between means was used for continuous variables and the OR was calculated for the other cases. For studies with statistical homogeneity the fixed effect model was used. The random effect model was considered for cases with a heterogeneity test value of $p < 0.10$.

All analyses were carried out using a significance level of $\alpha = 0.05$. Comprehensive Meta-Analysis software version 1.0.23 (Biostat, Englewood, NJ, USA) was used for this analysis.

Results

Systematic Review

This systematic review included ten published articles and one non-published report corresponding to a total of 13 clinical trials in the adult population (table I). Eleven studies compared the efficacy of pirlindole with another active comparator,[16-18,20-24,26] and two compared its efficacy with placebo[25,27] in the treatment of depression. The active comparators were amitriptyline, desipramine, fluoxetine, imipramine, maprotiline, mianserin and moclobemide. The study selection process is summarized in figure 1.

The study scores on the Jadad scale varied between 2 and 5, with a mean value of 3.7. From the 13 clinical trials selected, only one was classified on the Jadad scale as 2, because it did not state whether the study was randomized or not,[21] and five were classified as having a score of 3,[17,20,22,23] essentially due to a lack of information on how randomization was performed and on the reasons for the identified dropouts.

Meta-Analysis

All studies included in the meta-analysis reported data published between 1966 and August 2010 for a total of 776 patients. In addition, all

Table II. Description of randomized, double-blind, parallel-group, controlled trials involving pirlindole in the treatment of depression

Study	Total no. of patients	No. of patients treated with pirlindole	Inclusion criteria	Mean age (y)	Female patients (%)	Duration of treatment (days)	No. of dropouts	Reasons for dropout	Efficacy measures
Lehmann et al.[20]	39-In	19	HDRS ≥24; age >18 years	ND	ND	21	7 (3 pirlindole)	ND	HDRS
Renfordt[21]	21-In	11	ND	ND	76	28	ND	ND	Clinical criteria
Blaha[22]	30-In	15	ND	51	ND	21	4 (1 pirlindole)	ND	LTD; Erlangen scale
Schäpperle et al.[17]a	80-In	40	ND	40	25	42	10 (5 pirlindole)	Deterioration of clinical condition; no improvement; changing syndrome; patient decision; suicide attempt	HDRS; Immich scores; BDI
Schäpperle et al.[17]b	80-In	40	ND	35	16	21	10 (7 pirlindole)	ND	HDRS; Immich scores; BDI
Saletu et al.[23]	50-Out	25	ND	41	56	21	Unknown	ND	HDRS; Zung Self-Rating Scale
Pöldinger[24]	40-Out	20	Acute phase depression	43	70	21	12 (5 pirlindole)	Very good improvement; aggravation; adverse effects; exacerbation of schizophrenic symptoms; patient's decision	HDRS; Scale for General Psychological Findings
Tanghe et al.[18]c	111-In and out	52	DSM-III-R diagnosis; HDRS (17-item) ≥18	45	68	42	34 (17 pirlindole)	Lost to follow-up; adverse effects; inefficacy; patient's decision	HDRS; HARS; MADRS
De Wilde et al.[25]	98-In	49	DSM-III-R diagnosis; HDRS (21 item) ≥18 and MADRS ≥25	46	70	42	39 (20 pirlindole)	Symptoms remission; adverse effects; aggravation of depression	HDRS; HARS; MADRS
De Wilde et al.[16]	40-In	20	HDRS (21 item) ≥24	51	75	28	2 (2 pirlindole)	Shift to mania; inefficacy	HDRS; HARS; BDI
Geerts et al.[26]c	208-In and out	104	DSM-III-R diagnosis; HDRS (17-item) ≥18	43	65	42	43 (24 pirlindole)	Inefficacy; adverse effects; lost to follow-up; intercurrent pathology; pregnancy	HDRS; HARS; MADRS
Geerts et al.[26]c,d	65-In and out	28	DSM-III-R diagnosis; HDRS (17-item) ≥18	ND	ND	180	17 (10 pirlindole)	Unsatisfactory response; advanced improvement: patient decision	HDRS; clinical criteria
Zapletálek et al.[27]	30-Out	14	Endogenous depression diagnosis; HDRS ≥20	44	83	35	9 (4 pirlindole)	Inefficacy; patient's decision; adverse effects	BPRS; CGI; HDRS; HARS; DVP

a Comparator was amitriptyline.

b Comparator was imipramine.

c Some of the patients included in this study had depressive episodes associated with bipolar disorder.

d Follow-up of subgroup of patients included in the study above.

BDI = Beck Depression Inventory; **BPRS** = Brief Psychiatric Rating Scale; **CGI** = Clinical Global Impressions; **DSM-III-R** = Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised; **DVP** = Vinar's Complemented Scale of Side Effects; **HARS** = Hamilton Anxiety Rating Scale; **HDRS** = Hamilton Depression Rating Scale; **In** = inpatients; **LTD** = Leistungstest für depression; **MADRS** = Montgomery-Åsberg Depression Rating Scale; **ND** = not determined; **Out** = outpatients.

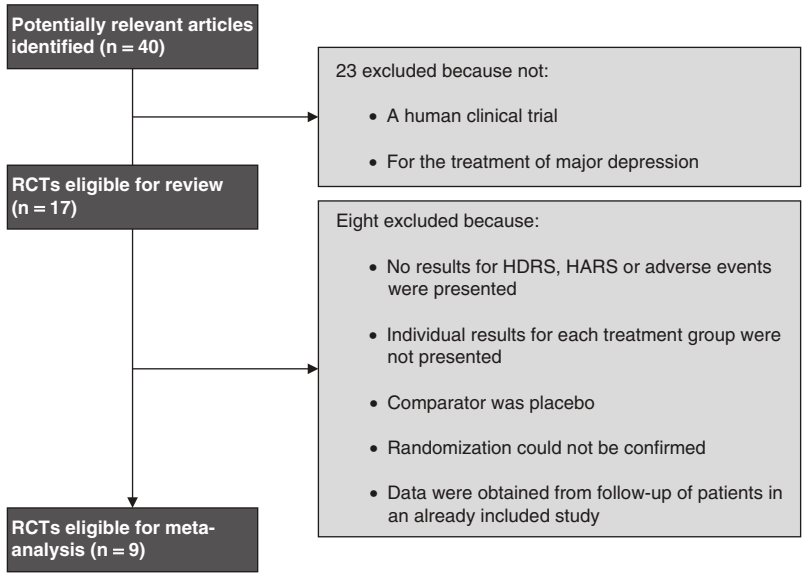

Fig. 1. Flow diagram of selected randomized controlled trials (RCTs). **HARS** = Hamilton Anxiety Rating Scale; **HDRS** = Hamilton Depression Rating Scale.

studies included in the meta-analysis met the homogeneity criterion. Their main characteristics are described in table I and table II. Nine studies were included in the meta-analysis. The study by Renfordt[21] was excluded because it was not clear whether or not it was randomized (Jadad scale 2). Only the studies that compared pirlindole with active comparators were included in this meta-analysis, and, therefore, studies that compared pirlindole with placebo were excluded. Also, to minimize the risk of bias, only randomized, double-blind studies with HDRS and HARS scores as efficacy endpoints or with reported adverse events were included. Moreover, one of the clinical trials,[26] despite fulfilling the inclusion criteria, was not considered for this meta-analysis as it was an extension of the other non-published clinical trial reported in the same article with results corresponding to follow-up of patients who continued the treatment for another 6 months.

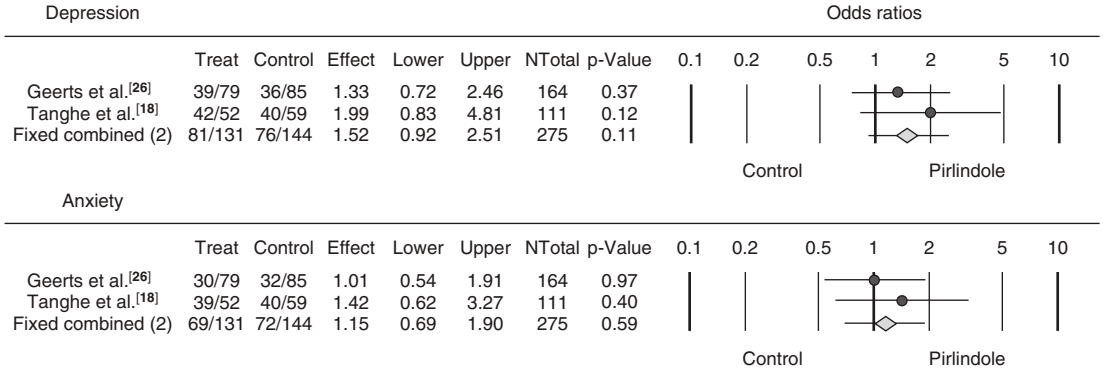

Fig. 2. Percentage of patients that improved by 50% on the Hamilton Depression Rating Scale (top) and Hamilton Anxiety Rating Scale (bottom) with 95% confidence interval for treatment (pirlindole) vs control groups. **Lower** = lower confidence limit; **NTotal** = total number of patients; **Treat** = treatment; **Upper** = upper confidence limit.

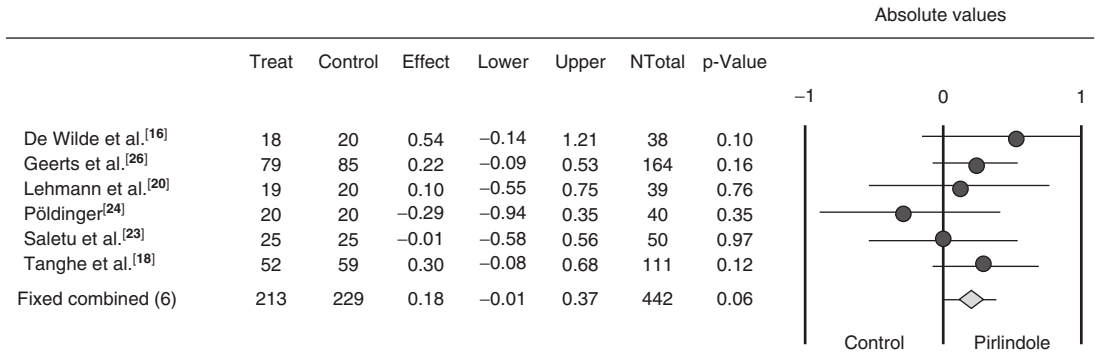

Fig. 3. Improvement on the Hamilton Depression Rating Scale with 95% confidence interval for treatment (pirlindole) vs control groups. **Lower** = lower confidence limit; **NTotal** = total number of patients; **Treat** = treatment; **Upper** = upper confidence limit.

Two of the included studies[18,26] evaluated patients with depressive episodes associated with bipolar disorder. In the RCT by Tanghe et al.[18] only 21% of pirlindole recipients and 22% of moclobemide recipients presented with this disorder. In the other trial by Geerts et al.,[26] only one patient with bipolar disorder was included in the fluoxetine group, representing approximately 1% of all patients.

In figures 2 to 4, pirlindole is shown to be more effective than its comparator(s) whenever the results fall to the right of the centre of the graph. For absolute values (figures 3 and 4), the effect statistic represents the difference between the effect of pirlindole and the effect of the active comparator for the parameter under evaluation. Whenever the effect is above zero and the confidence interval (CI) does not include this value, the results are favourable for pirlindole. For OR values, the effect statistic represents the ratio between the proportions for each group (pirlindole and active comparator[s]). Whenever the effect is above 1 and the CI does not include this value, the results are favourable for pirlindole.

All the meta-analyses carried out compared the effect of pirlindole with that of an active comparator in adult patients with major depression or with a depressive episode in patients with bipolar disorder. The studies included were relatively homogeneous in terms of therapeutic indication, patients' demographic characteristics and treatment duration (table II). The calculated heterogeneity test values were $p > 0.10$ (95% CI) for all of the analysed studies, and therefore the fixed effect model was used for all the included trials.

The percentages of patients whose clinical condition improved by 50%, as assessed by the HDRS and HARS, were reported in two clinical trials.[18,26] Figure 2 shows the OR results for this parameter. No statistically significant differences

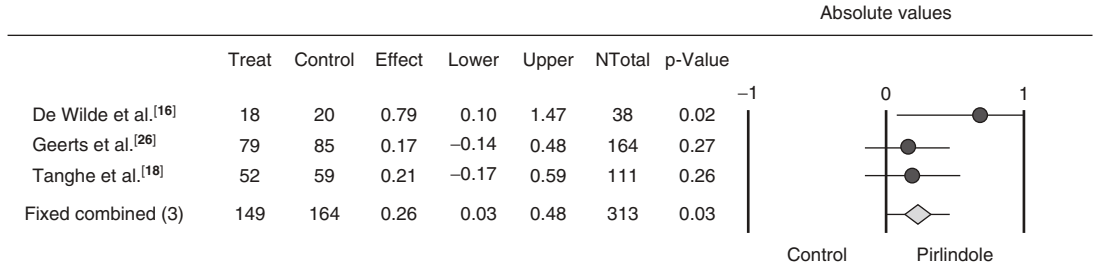

Fig. 4. Improvement on the Hamilton Anxiety Rating Scale with 95% confidence interval for treatment (pirlindole) vs control groups. **Lower** = lower confidence limit; **NTotal** = total number of patients; **Treat** = treatment; **Upper** = upper confidence limit.

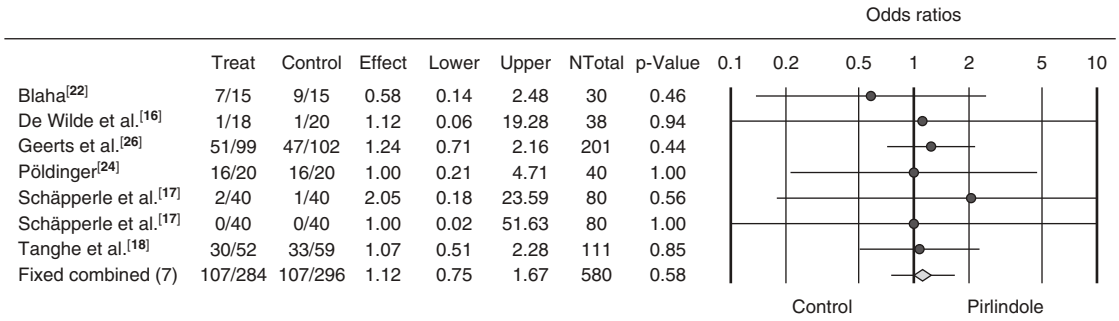

Fig. 5. Percentage of patients with adverse events with 95% confidence interval for treatment (pirlindole) vs control groups. The two entries for Schäpperle et al.[17] represent comparisons of pirlindole with two different comparators reported in this article. **Lower** = lower confidence limit; **NTotal** = total number of patients; **Treat** = treatment; **Upper** = upper confidence limit.

were found between pirlindole and its comparators (moclobemide and fluoxetine) [p = 0.11 and p = 0.59, respectively].

The mean variation in HDRS was reported in six clinical trials,[16,18,20,23,24,26] corresponding to 442 patients. In four[16,18,20,26] of these six RCTs the effect is above zero, favouring pirlindole in terms of absolute values; however, the results were not significantly different between groups (p = 0.06) [figure 3]. On the other hand, the scale for anxiety (HARS), used in three clinical trials,[16,18,26] showed positive results for pirlindole (figure 4) [p = 0.03].

The percentage of patients with adverse events was reported in seven studies,[16-18,22,24,26] corresponding to a total of 580 patients. The most commonly reported adverse events with pirlindole treatment were dry mouth and sleep disturbances. No statistically significant differences between pirlindole and the active comparators (amitriptyline, imipramine, maprotiline, moclobemide, mianserin and fluoxetine) were found (figure 5) [p = 0.58]. No serious adverse reactions to pirlindole were reported.

Discussion

The main objective of this review was to select the best evidence to evaluate the efficacy and frequency of adverse events with pirlindole in the treatment of major depression. Therefore, a detailed analysis of published and non-published RCTs was performed.

This review provides an overview of evidence on pirlindole compiled by gathering the best available clinical evidence and pooling data from small clinical trials, thereby providing more consistent, comprehensive and accurate estimates of the drug's treatment effects. To achieve this, clinical trials with methodological limitations, such as those that did not present individual results for each treatment group or that did not allow confirmation of randomization, were excluded from this meta-analysis to minimize inaccuracies in the results. However, some limitations of the RCTs selected for this meta-analysis can still be identified. These include the wide range of active comparators used in each study, the small number of patients enrolled in the majority of the studies, and the lack of methodological information available, particularly in relation to reasons for dropouts and results for each endpoint. However, while the number of dropouts identified in studies is an important consideration, and one that can influence the results of each study independently, the differences between pirlindole and its active comparators in terms of numbers of dropouts did not appear to impact on the results of this meta-analysis. Another possible limitation was that two of the included RCTs[18,26] reported data on patients with bipolar disorder. However, the numbers of patients with this disorder were small (1% and 22% of the study populations), and the data for these patients, therefore, had only a small impact on the results of the meta-analysis.

The small number of included RCTs evaluating HDRS and HARS endpoints was also a limitation of this meta-analysis. Despite these limitations, in general, the included articles were of a reasonable methodological quality, with a mean value of 3.7 on the Jadad scale (range 0–5).

All of the nine RCTs selected for meta-analysis included adult patients with major depression and bipolar disorder. Pirlindole was used in doses of 150–450 mg/day, with 225 mg/day being the most common dose (given as 75 mg three times daily). The active comparators studied were MAOIs (moclobemide), tricyclic antidepressants (amitriptyline, desipramine and imipramine), tetracyclic antidepressants (maprotiline and mianserin) and SSRIs (fluoxetine). In addition, two of the studies in the systematic review compared pirlindole with placebo.

An important finding of this meta-analysis is that pirlindole was not significantly different in efficacy to the active comparators used to treat depression. Moreover, according to the HARS, pirlindole was actually more effective than its comparators. These results are consistent with findings from other published studies that show the benefits of MAOIs in some anxiety disorders.[6,8] However, further studies with more rigorous methodology, a larger number of patients and more recently introduced comparators should be conducted.

The meta-analysis also showed that pirlindole was not significantly different from its active comparators in terms of tolerability, given the similar number of adverse events reported for both pirlindole and its active comparators. The most commonly reported adverse events of pirlindole were dry mouth and sleep disturbances, and no serious adverse reactions to the medication were reported.

Conclusion

Notwithstanding the small number of RCTs published to date assessing the efficacy and general tolerability profile of pirlindole and the methodological quality of these trials (Jadad scale mean score 3.7 of 5), this systematic review and meta-analysis showed that all RCTs that have been conducted reported efficacy outcomes for pirlindole comparable to those of its comparators, and with significantly better results in the reduction of anxiety symptoms. Moreover, no significant differences were found between pirlindole and its active comparators in terms of the frequency of adverse events or in all other evaluated efficacy parameters.

Acknowledgements

Grupo Tecnimede markets pirlindole in Portugal and funded the conduct of this meta-analysis and the preparation of this article.

Ana Macedo, MD, PhD, and Eva Leiria, MS, work as scientific advisers at KeyPoint, Consultoria Científica, Lda. Augusto Filipe, MD, is an employee of Grupo Tecnimede and reviewed the final manuscript. The authors have no other conflicts of interest that are directly relevant to the content of this meta-analysis.

The authors wish to thank Ana Maria Tomé, PharmD, and Inês Moital for assistance in the revision of the article and Liliana Coelho for assistance in the management of the manuscript submission and bibliographic research.

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