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Pindolol augmentation of serotonin reuptake inhibitors for the treatment of depressive disorder: a systematic review

R Whale *Institute of Postgraduate Medicine, Brighton and Sussex Medical School, Brighton, UK.*
T Terao *Department of Neuropsychiatry, Oita University, Oita, Japan.*
P Cowen *Department of Psychiatry, University of Oxford, Oxford, UK.*
N Freemantle *Health Care Evaluation Group, University of Birmingham, Birmingham, UK.*
J Geddes *Department of Psychiatry, University of Oxford, Oxford, UK.*

Abstract

Adding pindolol to serotonergic antidepressant treatment offers a potential strategy for producing a more rapid onset of action and an enhanced antidepressant effect. This review investigated whether pindolol enhances the efficacy of serotonergic antidepressant treatment in adult patients with depressive disorders at sequential time points up to 6 weeks. *Search strategy*: Cochrane Collaboration Depression, Anxiety and Neurosis-Controlled Trials Register plus unpublished trial data. *Study selection*: Randomised trials including depressed patients, comparing serotonergic antidepressants + pindolol with serotonergic antidepressants + placebo and using depressive symptom clinical outcomes scales. *Data extraction*: Clinical response at time points up to 6 weeks as defined by >50% depression scale score reduction was extracted for each trial as possible. Eleven studies were identified including unpublished data. The pooled odds ratios for dichotomous response to treatment at time points from 1 to 6 weeks were 2.39 (95% CI 1.40–4.06), 2.39 (1.74–3.29), 1.94 (1.46–2.58), 1.59 (1.16–2.18), 1.42 (0.87–2.31) and 1.28 (0.91–1.81). Time-to-event analysis showed a greater response with pindolol augmentation versus placebo ($P = 0.04$). There was significant heterogeneity between studies at some time points. Dropout rates did not significantly differ between treatment arms. This review suggests an overall beneficial clinical effect of pindolol augmentation, most clearly up to 4 weeks of treatment.

Key words
depressive disorder; pindolol; SSRI; systematic review

Introduction

Despite advances in the treatment of depressive disorders, available antidepressants take at least 2–3 weeks to produce a substantial clinical response and are not effective in all patients (Blier and de Montigny, 1994). Several open-label studies have investigated the efficacy of pindolol in combination with serotonergic antidepressants, showing a more rapid onset of action and enhanced antidepressant effect (Artigas, *et al*., 1994; Blier and Bergeron, 1995; Vinar, *et al*., 1996). This could offer substantial clinical benefit in depressed subjects, particularly in those who are suicidal or restricting fluid and food intake as symptoms of their illness. However, results from randomised, placebo-controlled, double-blind studies of pindolol combination have been inconsistent, and no definite conclusion of its effects has been established (McAskill, *et al*., 1998). The review by Ballesteros and Callado (2004) included nine trials, showed equal tolerability and adverse event rate with pindolol versus placebo and suggested a beneficial effect of pindolol augmentation at 2 weeks but not at 4–6 weeks of treatment.

In addition to its ability to block β-adrenoceptors, pindolol also binds to serotonin$_{1A}$ (5-HT$_{1A}$) receptors. Indeed, the clinical effect of pindolol augmentation of antidepressant treatment is hypothesised to be mediated by antagonism of 5-HT$_{1A}$ autoreceptors on 5-HT cell bodies. Animal electrophysiology studies show that 5-HT potentiating antidepressant drugs enhance neurotransmission across 5-HT synapses after chronic but not acute administration (de Montigny and Blier, 1984; Blier, *et al*., 1990). 5-HT$_{1A}$ autoreceptors are involved in the inhibition of 5-HT cell firing and are activated by acute

Corresponding author: Richard Whale, IPGM, Brighton and Sussex Medical School, Falmer, Brighton BN1 9PH, UK. Email: richard.whale@brighton.ac.uk

administration of 5-HT potentiating antidepressants such as selective serotonin reuptake inhibitors (SSRIs). Continued administration of the antidepressant leads to desensitisation of 5-HT_{1A} autoreceptors resulting in greater enhancement of 5-HT neurotransmission by the antidepressant. Therefore, antagonism of the 5-HT_{1A} receptor from the start of antidepressant treatment would be expected to produce an earlier and greater enhancement of serotonergic neurotransmission and antidepressant activity (Artigas, *et al*., 1994).

This review aimed to investigate whether pindolol enhances the efficacy of antidepressant treatment in adult patients with depressive disorders at different time points up to 6 weeks.

Methods

Data source

The search strategy for identification of studies was as follows:

1) Electronic databases: The Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register (CCDANCTR), incorporating results of group researches of MEDLINE (1990-April 2007), EMBASE (1990-April 2007), CINAHL (1990-April 2007), PsycLIT (1990-April 2007), PSYNDEX (1990-April 2007) and LILACS (1990-April 2007) was searched using the following terms: #45 (diagnosis field) = depression or depressive-disorder and # (intervention field) = pindolol or visken or viskaldix or visten or barbloc or novo-pindol or nu-pindol or durapindol or glauco-stulln or pectobloc or pinbelol or pindoptan or pindoreal or viskeen or decreton or hexapindol or bedrenal or betapindol or viskene or viskenit or viskezide or nitrisken.
   The Cochrane library was also searched using the same terms as for CCDANCTR excluding references tagged with sr-depress as these have come from CCDANCTR.
2) References checking: The reference lists of all selected studies were inspected for more published reports and citations of unpublished research. In addition, other relevant papers and major textbooks that cover affective disorders were checked.
3) Personal communications: To ensure all randomised trials are being identified, the authors of significant papers and other experts in the field were contacted as necessary.
4) Pharmaceutical companies: Pharmaceutical companies manufacturing antidepressant medication were contacted to find out if they knew of any published or unpublished randomised controlled trials (RCTs) relevant to this review. Reviewers RW and TT undertook this search.

Study selection

Studies included in this review met the following criteria:

1) Types of studies: Prospective randomised controlled trials (RCTs).
2) Participants: All patients suffering from a depressive disorder according to explicit criteria, including major depressive disorder (unipolar depressive disorder) and bipolar depressive disorder.
3) Interventions: Studies comparing the effect of pindolol against placebo in combination with SSRIs for antidepressant treatment.
4) Outcome measures: Dichotomous clinical response, as defined by >50% depression scale score reduction. We intended to extract this data for different time points up to 6 weeks to examine differences of antidepressant effect between treatment arms.

The methodological quality of included studies was independently assessed by reviewers RW and TT. Quality was assessed according to the Cochrane criteria for quality assessment (Sackett, 1997), focussing particularly on the quality of the randomisation procedure and allocation concealment. On this basis, studies were given a quality rating of A (adequate), B (unclear) and C (inadequate). If the raters disagreed, the final rating was made by consensus with the involvement, if necessary, of another review group. Other key aspects of randomised controlled trial quality such as whether the trial was of a double-blind design and reporting of withdrawals and dropouts were assessed. Where adequate details of randomisation and other characteristics of trials were not provided, the authors were contacted to obtain further information.

Data extraction

Data were extracted about participant characteristics, intervention details and outcome measures from the included studies. Any disagreement was resolved by consensus discussions. Last observation carried forward was adopted for dropouts at all stages of trials. Dropouts were counted as non-responders in the binary efficacy outcome measure.

Data were entered into Review Manager 4.2 software by two reviewers using the duplicate data entry facility. For the binary efficacy outcome, a pooled odds ratio (OR) with 95% confidence intervals (CI) was calculated using a fixed effects model. Heterogeneity between studies was assessed using the Q statistic (DerSimonian and Laird, 1986) and I^2 (Higgins, *et al*., 2003). If significant heterogeneity was identified, sources were investigated. Random effects models were used routinely to investigate the sensitivity of results to the choice of statistical method. Outcome was measured at different time points up to 6 weeks (at 1, 2, 3, 4, 5 and 6 weeks). The influence of refractory depressive syndrome, severity of illness at admission to the trials, type and dose of serotonergic antidepressant and dose of pindolol on study outcome were intended to be explored. A time-to-event analysis was also undertaken, using a discrete logistic model, using cumulative response data at each weekly time point, to examine whether pindolol augmentation was associated with a greater response than placebo. The discrete logistic model accounted for trial as a fixed effect and examined the validity of the assumption of constant proportional hazards. The time-to-event analysis was conducted in SAS 9.1 (SAS Institute, Cary, North Carolina, USA).

Results

Overall, 11 studies met criteria for inclusion in this review and their characteristics, including methodological quality, are shown in Table 1. Nine studies were identified from electronic databases Berman, *et al*. (1997, 1999), Bordet, *et al*. (1998), Maes, *et al*. (1999), Perez, *et al*. (1997, 1999), Tome, *et al*. (1997) and Zanardi, *et al*. (1997, 1998). For one additional study identified electronically but not including responder data in the paper, the authors were contacted who kindly supplied this data to us by email (Zanardi, *et al*., 2001). One unpublished study was discovered by approaching pharmaceutical companies (Holland, *et al*., 1997). Despite other companies planning such studies, no further evidence of completed trials was found.

Absolute continuous values of depression scale scores were not available in the published accounts of these identified studies, and key authors contacted were unwilling to share this data. Data availability at weekly time points up to 6 weeks varied between these studies. Only subjects fitting inclusion criteria for this review within each study were included (e.g., a mianserin treatment arm in the Maes, *et al*. study (1999) was excluded, as mianserin is not an SSRI), and we endeavoured

Table 1 Characteristics of randomised controlled trials including depressed patients comparing serotonin reuptake inhibitors with pindolol versus serotonin reuptake inhibitors with placebo, accepted for this reviews

Study	Included subjects	Age (years)	Duration (days)	Participant characteristics	Intervention	Dropouts (pindolol arm)	Method quality rating
Berman, *et al*. (1997)	43	18–70	42	DSMIV Major Depression HAMD (25 item) ≥18 Non-psychotic outpatients	Fluoxetine 20 mg + Pindolol 5 mg bd or 2.5 mg tds versus placebo	8 (3)	A
Berman, *et al*. (1999)	43	18–70	42	DSMIV Major Depression HAMD (25 item) ≥18 Non-psychotic outpatients (only new data from report included)	Fluoxetine 20 mg + Pindolol 2.5 mg tds vs placebo	9 (4)	A
Bordet, *et al*. (1998)	100	18–65	21	DSMIV Major Depression unipolar HAMD (17 item) ≥18 Non-psychotic in and out patients	Paroxetine 20 mg + Pindolol 2.5 mg tds vs placebo	20 (10)	A
Holland, *et al*. (1997)	164	18–65	42	ICD10 Depression MADRS ≥18 Non-psychotic outpatients	Paroxetine 20 mg + Pindolol 2.5 mg tds versus placebo	22 (11)	A
Maes, *et al*. (1999)	21	25–70	35	DSMIIIR Major Depression HAMD (17 item) ≥16 Inpatients	Fluoxetine 20 mg + Pindolol 2.5 mg tds versus placebo	not recorded	A
Perez, *et al*. (1997)	111	over 18	42	DSMIV Major Depression unipolar HAMD (17 item) ≥18 Non-psychotic outpatients	Fluoxetine 20 mg + Pindolol 2.5 mg tds versus placebo	22 (9)	A
Perez, *et al*. (1999)	80	18–65	10	DSMIV Major Depression HAMD(17 item) ≥16 Non-psychotic or bipolar outpatients Current episode resistant to SSRI but <9 months duration	SSRI + Pindolol 2.5 mg tds versus placebo	2 (1)	A
Tome, *et al*. (1997)	80	18–65	42	ICD10 Depression MADRS ≥18 Non-psychotic or bipolar outpatients	Paroxetine 20 mg + Pindolol 2.5 mg tds versus placebo	19 (8)	A
Zanardi, *et al*. (1997)	42	18–65	28	DSMIV Major Depression recurrent HAMD ≥18 Inpatients	Paroxetine 20 mg + Pindolol 2.5 mg tds versus placebo	0 (0)	A
Zanardi, *et al*. (1998)	72	18–65	42	DSMIIIR Major Depression HAMD ≥ 21 Delusion experience scale >3 Psychotic Inpatients Including bipolar	Fluvoxamine increased to 150 mg bd over 8 days + Pindolol 2.5 mg tds versus placebo	1 (1)	A
Zanardi, *et al*. (2001)	155	18–65	42	DSMIV Major Depression recurrent HAMD(21 item) ≥21 Inpatients Including bipolar and psychotic	Fluvoxamine increased to 150 mg bd over 8 days + Pindolol 2.5 mg tds versus placebo	5 (1)	A

not to count subjects twice within identified republished data (as with Berman, *et al*., 1999). All studies used the Hamilton Depression Symptom Rating Scale (HAMD) except Holland, *et al*. and Tome, *et al*. who used the Montgomery Asberg Depression Rating Scale (MADRS). All studies allowed concomitant benzodiazepines only except the first Zanardi, *et al*. trials (1997, 1998) that allowed no concomitant medication and the later Zanardi, *et al*. trial (2001) that included a small group on lithium maintainance and allowed benzodiazepine use. The Zanardi, *et al*. (1997, 1998, 2001), Maes, *et al*. (1999) and Perez, *et al*. (1997, 1999) studies included a placebo run-in before starting antidepressant/pindolol.

Exceptions to available data on dichotomous 50% reduction in depression scale score at specific weekly time points were as follows. In the Bordet, *et al*. (1998) study, percent of patients 'remitting' was defined as a HAMD (17 item) score of ≤10. This was deemed adequately equivalent to at least a 50% reduction in HAMD score and data at days 5, 10 and 21 were entered in this review at weeks 1, 2 and 3, respectively. For the Perez, *et al*. (1999) trial, number of 'responders' at day 10 was entered for day 14. For the included Zanardi, *et al*. studies (1997, 1998, 2001), numbers of responders at weekly time points were classified as those achieving a HAMD of <8. These assumptions made are all likely underestimates of actual 50% depression scale score reductions.

All included trials were assessed to have adequate quality of randomisation and allocation concealment and rated as 'A'. There was no disagreement about trial quality ratings between reviewers.

A total of 889 subjects were included in these trials with 435 receiving pindolol and 454 receiving placebo. Dichotomous outcomes of numbers of subjects in each arm reaching at least a 50% reduction in depression rating scale were available or interpretable (as above) for these trials, although not consistently at all time points up to 6 weeks. Figure 1 plots the data obtained for weeks 1–6 individually. The fixed effects pooled ORs (95% CI) for treatment after 1, 2, 3 and 4 weeks consistently favoured the pindolol treatment arm and were 2.39 (1.40–4.06), 2.39 (1.74–3.29), 1.94 (1.46–2.58) and 1.59 (1.16–2.18), respectively. The ORs (95% Confidence Interval) for weeks 5 and 6 were not statistically significant at 1.42 (0.87–2.31) and 1.28 (0.91–1.81), respectively, although the direction of the effect was towards benefit for pindolol. By week 6, the number of trials contributing data had reduced from 10 (at week 2) to 7, and the corresponding number of subjects included in the analysis had reduced from 710 at week 4 to 667 at week 6. Furthermore, the binomial distribution has a bigger variance when the incidence rate approaches 50%. Thus, the absence of evidence of effect at 5 and 6 weeks may be artefactual. Examining random effects models for pooled OR showed similar statistically significant beneficial effects of pindolol over placebo for weeks 1–4 (all CI > 1) only. The numbers needed to treat for weeks 1–4 are 16, 7, 7 and 12, respectively.

The hazard ratio for time to response for pindolol versus placebo augmentation was 1.26 (95%CI 1.01–1.58; $P = 0.04$), modestly significantly favouring pindolol. For the proportional hazards assumption violation test, $P = 0.96$, indicating no evidence for a departure from linearity in effect. Figures 2 and 3 show the cumulative response and survival analysis graphs.

Dropouts

In the trials that included data on dropouts (all except the Maes, *et al*. (1999) trial), 48/435 (11%) and 60/454 (13%) dropped out of the pindolol and placebo arms, respectively (chi squared = 0.99, $P = 0.31$). An investigator group effect is observed, with the Zanardi, *et al*. studies (1997, 1998, 2001) showing much lower dropout rates of 2% for pindolol and 3% for placebo arms. Descriptions of dropouts in these included studies were not consistently adequate to undertake further sensitivity analysis (all dropouts in either arm were assumed to be non-responders).

Heterogeneity

There was statistically significant (at $P < 0.1$ level) heterogeneity between the trial-specific estimates at weeks 2, 3, 4 and 5 with varying degrees of inconsistency between studies measured by I^2. The later Berman, *et al*. trial (1999) was most consistently discrepant (favouring placebo). Random effects estimates were calculated to take account of the heterogeneity and were broadly similar to the fixed effects estimates at all time points.

We explored the potential role of several study level characteristics in exploring this heterogeneity:

Refractory depressive syndrome Most studies included a mix of refractory and non-refractory subjects. Perez, *et al*. (1999) examined augmentation of existing SSRI treatment to which subjects had not responded to a reasonable trial, with no overall significant positive outcome. Perry, *et al*. (2004) described no significant benefit of randomised pindolol augmentation in patients who had not responded to an adequate previous trial of an SSRI (this study was not included in this review as the authors have not clarified whether these subjects were included in the previously published Berman, *et al*. studies that were undertaken around the same time). Maes, *et al*. (1999), however, included a subanalysis of treatment resistant subjects (non-response to a single previous adequate trial with an antidepressant) comprising 15 patients and showed a significant benefit of pindolol augmentation in this small group. Sokolski, *et al*. (2004) also showed a beneficial response to once daily pindolol augmentation (7.5 mg) in a small group ($n = 9$) of previous SSRI non-responders (the authors have not supplied further details of this trial to enable inclusion in this review). The overall influence of refractory syndrome on pindolol response is therefore unclear. The response to pindolol in non-refractory subjects was unable to be ascertained.

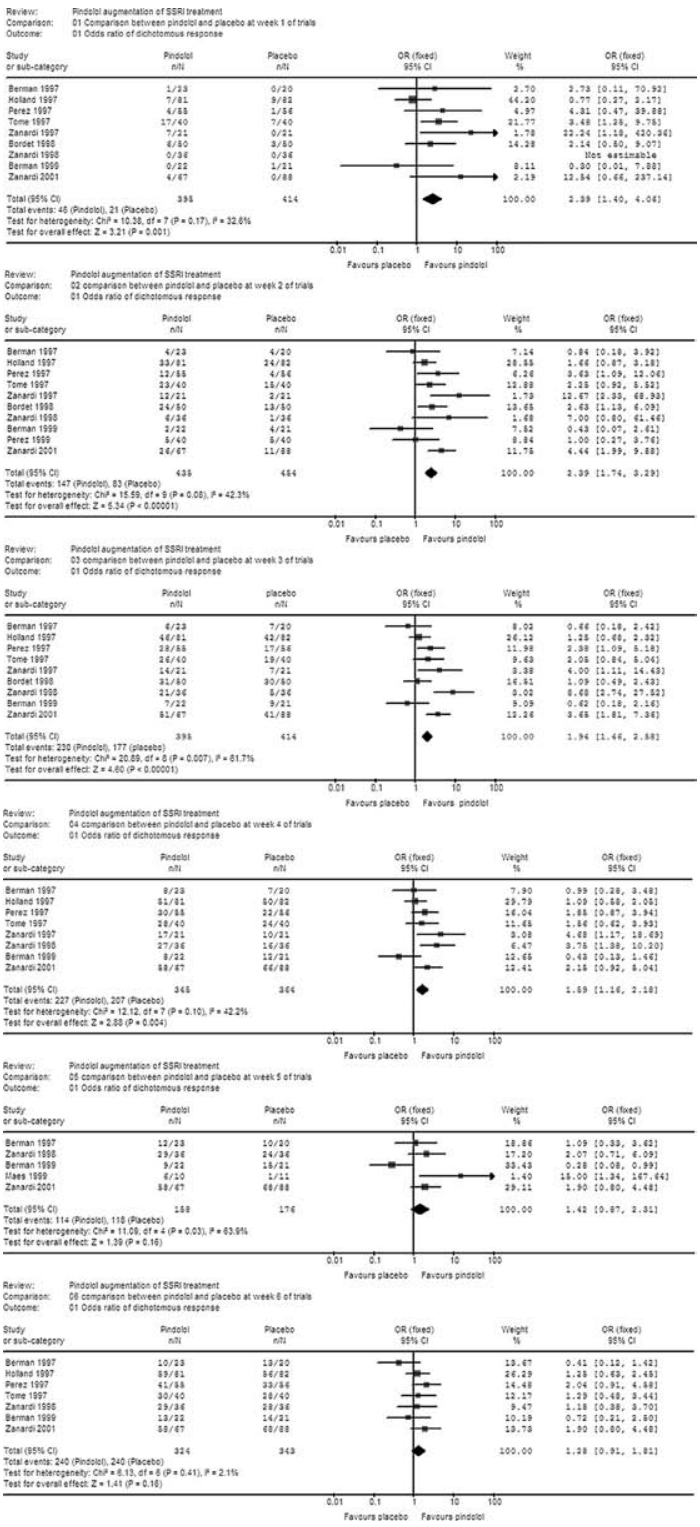

Figure 1 Plots of dichotomous response to randomised pindolol versus placebo augmentation of serotonin reuptake inhibitors in depressed subjects by weeks 1–6. Response is defined as a 50% improvement in depressive scale score. *n*, number of responders; *N*, number of patients per group; OR, odds ratio.

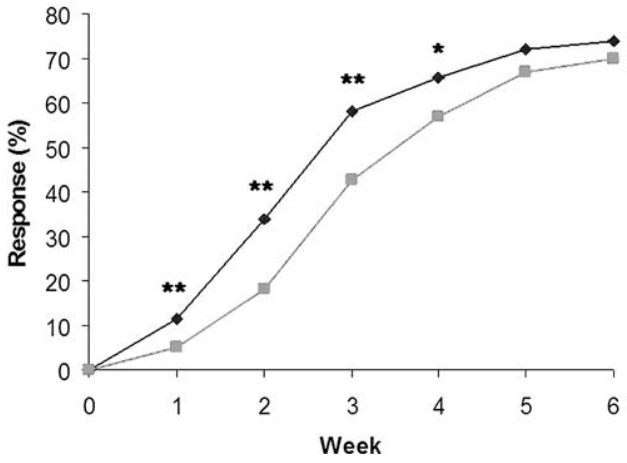

Figure 2 Cumulative response (50% improvement of depression scale score) to augmentation of serotonin reuptake inhibitors with randomised pindolol (diamonds) versus placebo (squares) in depressed subjects by time. *$P < 0.025$, **$P < 0.001$; chi squared for pindolol versus placebo.

Severity of illness at admission to the trials Inpatients [as included in trials by Zanardi, *et al*. (1997, 1998, 2001) and Maes, *et al*. (1999)] appeared to show more beneficial responses to pindolol than outpatients included in other trials. This could equally be an investigator group effect. The only trial examining solely psychotic depressed subjects showed overall significantly beneficial effects with pindolol at weeks 3 and 4 (Zanardi, *et al*., 1998). This delay in response to week 3 may relate to the titration period of fluvoxamine in this trial. Data available were not adequate to correlate response with depression symptom scale scores at inclusion. The study by Tome, *et al*. (1997) showed a site effect within the trial, with the better responding clinic having less severe and chronic depression and more previously untreated subjects. Studies including subjects with higher range baseline HAMD scores (mean > 30) were Berman, *et al*. (1997, 1999) and Zanardi, *et al*. (1998, 2001), which showed no within group consistent effect of pindolol augmentation. The overall influence of severity of illness on pindolol response is therefore also unclear.

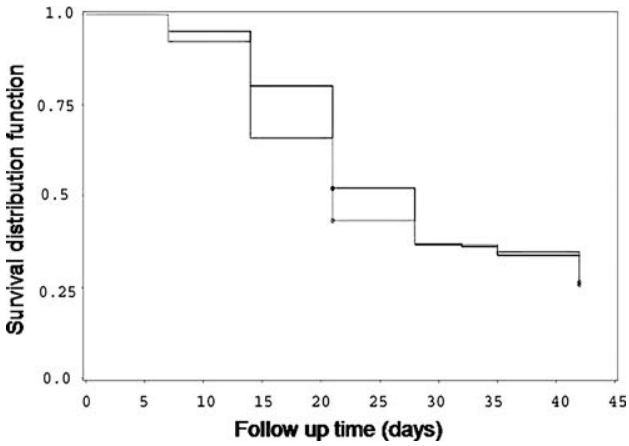

Figure 3 Survival plot of response (50% improvement of depression scale score) to augmentation of serotonin reuptake inhibitors with randomised pindolol (red line) versus placebo (blue line) in depressed subjects by time.

Type and dose of serotonergic antidepressant The only consistent effect of type of SSRI was that the two trials using fluvoxamine [both by Zanardi, *et al*. (1998, 2001)] had associated significant effect of adding pindolol. This could also be a site effect. Other trials showed varying effects within SSRI groups. Plenge and Mellerup (2003) have argued that using paroxetine in combination with pindolol is the most effective SSRI choice, but this is not consistently borne out from the data presented here. The influence of dose of SSRIs could not be examined because of no variation between trials.

Dose of pindolol Only one included study (Berman, *et al*., 1997) varied in the dose of pindolol used from 2.5 mg tds, with 9 of 43 subjects receiving 5 mg bd. The overall influence of pindolol dose could, therefore, not be examined although PET imaging evidence suggests that the dose 2.5 mg tds does not produce reliable occupancy of 5-HT_{1A} receptors in the human brain (Rabiner, *et al*., 2001). Sokolski, *et al*. (2004) used once daily pindolol dosing of 7.5 mg with beneficial effects (further details of this trial were not supplied to enable inclusion).

Other factors Other relevant factors influencing heterogeneity may include the use of placebo run-in (which six trials included as above), but this appeared to have no influence and was deemed to be unimportant when analysed using survival analysis by Perez, *et al*. (2001). In a descriptive review, Segrave and Nathan (2005) concluded that untreated patients with few previous depressive episodes, less duration of current episode and no other psychiatric comorbidity would be more likely to respond to pindolol augmentation, but this is not clearly supported from the data in this review and would need to be examined in specific trials to be clarified. Genetic influences, such as the 5-HT transporter 44 base pair insertion/deletion polymorphism (Smeraldi, *et al*., 1998), could also influence response.

Conclusions

The use of pindolol to augment SSRI treatment has theoretic appeal and support from animal experimental studies. However, the results of clinical randomised trials have appeared inconsistent. This review includes a larger study sample than those previously published (e.g., Ballesteros and Callado (2004) who included 594 subjects). The findings modestly sup-

port augmentation of newly started serotonergic antidepressant treatment with pindolol, particularly where fast onset is important, as it appears to increase the rate of response to treatment (with a favourable NNT of 7 at week 2), and it appears as well tolerated as placebo. The potential adverse effects of β-adrenoceptor blockade (particularly in respiratory and cardiac disorders) need to be weighed with the relatively transient benefit in antidepressant response.

Exploration of the greater heterogeneity at weeks 2–4, particularly the influence of selected illness and drug variables, was not conclusive because of limited published data and no further individual data available from study groups. No clear influence of type of patient (refractory depression or severity of depression at trial inception), choice of SSRI or pindolol dose on response was observed. The most influential predictor of outcome appeared to be study group.

Analysis by time to event indicates a benefit for pindolol without evidence of a departure from constant proportional hazards. However, when we consider the evidence from contingency table analysis at weeks 5 and 6 on their own, we do not see evidence of a treatment effect. The apparent loss of a clinically beneficial effect of augmentation after 4 weeks, if not a statistical artefact (as above), may reflect further synaptic adaptations that override initial enhanced 5-HT neurotransmission effects of 5-HT_{1A} autoreceptor blockade with pindolol. Tome, *et al*. (1997) and Berman, *et al*. (1999) indicated that withdrawal of pindolol after week 6 had no significant effect on depression scale scores, which influences how pindolol may be clinically used.

Wider clinical experience, beyond trial boundaries, has not overall led to favourable reports on the antidepressant effect of augmentation with pindolol. Perhaps, this is to be expected as antidepressant treatments already have overall observed small effects over placebo in clinical populations (Kirsch, *et al*., 2002) and compliance with taking pindolol three times per day could be poor. Clinicians adding pindolol following initial non-response to an antidepressant [as in the second Perez, *et al*. study (1999)] may also be unlikely to see further improvement, akin to the period after 4 weeks of pindolol augmentation of initial treatment when no further benefit is observed. A larger daily dose of pindolol may give greater clinical benefit as implied from imaging studies (Rabiner, *et al*., 2001).

Further larger trials and continuous data from existing pindolol studies, unavailable to the current authors, are required to confirm or refute the findings of this review. Additional studies could more specifically examine the time of onset of effect of pindolol, with daily monitoring of mood. More relevant to clinical practice, studies of pindolol versus placebo augmentation with more homogenous patient populations (e.g., severity of illness, refractory syndrome, naivety to treatment) would more clearly define who is likely to respond. This review focussed solely on clinical response, whereas longer term remission may be more clinically important and valuably studied.

Whether or not the beneficial effect of pindolol on rate of antidepressant response is due to 5-HT_{1A} receptor blockade remains to be established. If this is the case, development of more specific autoreceptor antagonists with greater clinical utility than pindolol, such as a longer half life, would be beneficial. Pindolol may have other properties, such as acting as a nitrogen species scavenger (Fernandes, *et al*., 2005), which could explain these effects.

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I chose this article because it is a systematic review consisting of 11 total articles for review that included randomized RCTs, a total patient number of 889 participants, discussing the efficacy of pindolol in use with SSRIs. The cohort group was of the largest size within a fairly recent time frame. Also, I appreciated that this meta-analysis specifically discussed how treatment with pindolol dwindled after week 4, this could be efficacious as a consideration for stopping therapy with pindolol and SSRI combination as the effects wear off quickly. Also, the discussion of the refractory depressive syndrome is discussed as part of this review, saying that for patients who did not initially respond to SSRI treatment in the first place, would not respond to the addition of pindolol to their depression medication regimen. Also, while this systematic review is on the older side, it was the largest cohort available and I felt it lent the highest level of evidence in this particular PICO instance. Ultimately this systematic review did point out that the transient benefit of pindolol in accelerating the patient's response to antidepressants may not be a strong enough benefit when weighing against possible beta-adrenoreceptor blockade adverse effects. While pindolol may not be efficacious long-term, it at least can help the patient to possibly feel less depressive symptoms at the beginning of their new SSRI treatment, where sometimes that may take more than 3 weeks to set in depending, of course, upon the patient themselves.