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Original article

A meta-analysis of clinical trials comparing the serotonin (5HT)-2 receptor antagonists trazodone and nefazodone with selective serotonin reuptake inhibitors for the treatment of major depressive disorder

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Abstract

Objective. — To compare response rates among patients with major depressive disorder (MDD) treated with either a serotonin-2 (5HT2-) receptor antagonist or a selective serotonin reuptake inhibitor (SSRI).

Methods. — Medline and PubMed were searched for double-blind, randomized clinical trials comparing either trazodone or nefazodone with an SSRI for the treatment of MDD. Data from 9 reports involving a total 988 patients were identified and combined using a random-effects model.

Results. — Patients randomized to treatment with a 5HT2 antagonist were as likely to experience clinical response as patients randomized to treatment with an SSRI (RR = 1.002, 95% CI: 0.85–1.17, $P = 0.978$). Pooled response rates for trazodone/nefazodone and the SSRIs were 61.1% and 61.7%, respectively. There was also no difference in overall discontinuation rates ($P = 0.334$), discontinuation due to adverse events ($P = 0.676$), or discontinuation due to inefficacy ($P = 0.289$) between the two groups.

Conclusions. — These results suggest that the 5HT2-receptor antagonists trazodone and nefazodone and the SSRIs do not differ with respect to their overall efficacy and tolerability in the treatment of MDD. Although the sample size was relatively large and conveyed sufficient statistical power to test for differences in the overall sample, depression is a heterogeneous condition and differences may exist between treatments in particular subgroups of patients.

Keywords: 5HT2; SSRI; Trazodone; Nefazodone; Depression

1. Introduction

The serendipitous discovery of the precursors of two of the major contemporary antidepressant families during the late 1950s, iproniazid for the monoamine oxidase inhibitors and imipramine for the tricyclic antidepressants (TCAs), has led to the subsequent development of numerous antidepressant compounds [25]. Unfortunately, however, many depressed patients continue to remain symptomatic despite several treatments [32]. In addition despite hundreds of clinical trials spanning over five and a half decades, known differences among available antidepressants are, generally, limited to aspects of safety and tolerability [25]. In line with this tradition, several double-blind, randomized studies published to date suggest no difference in the overall antidepressant efficacy between the following two major classes of antidepressants: agents which selectively inhibit the serotonin-2 (5HT2) receptor including trazodone and nefazodone with antidepressants which selectively inhibit the serotonin transporter and, thereby, inhibit the reuptake of serotonin (selective serotonin-reuptake inhibitors—SSRIs) in major depressive disorder (MDD) [4,5,6,9,10,16,17,23,33]. None of these studies, however, had adequate statistical power to detect small yet

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potentially meaningful differences in overall efficacy between the two treatment groups. In the absence of large, adequately powered trials, meta-analytical approaches can be used to assess relative efficacy by combining information from individual studies. Therefore, the purpose of this work was to conduct a systematic review and meta-analysis of all double-blind, randomized antidepressant trials comparing a 5HT2-receptor antagonist (i.e either trazodone or nefazodone) with a selective serotonin reuptake inhibitor (SSRI) for the treatment of MDD that have been published to date.

2. Methods

2.1. Data sources and search strategy

Studies were identified using searches of Pubmed/Medline. Searches were conducted by cross-referencing the terms ''trazodone'' or ''nefazodone'' with each of the six following terms: ''fluoxetine'', ''sertraline'', ''paroxetine'', ''fluvoxamine'', ''citalopram'', and ''escitalopram''. No language or year-of-publication limits were used.

2.2. Study selection

We selected for randomized, double-blind clinical trials comparing either trazodone or nefazodone with at least one SSRI for the acute-phase treatment of MDD. We then selected for studies which also met all of the following inclusion criteria:

1. Studies which used either the Hamilton Depression Rating Scale (HDRS) [15], the Montgomery–Asberg Depression Rating Scale (MADRS) [21], or the clinical global impressions/improvement scale (CGI) [14] as their primary outcome measure.
2. Reports describing original data (i.e. containing data published elsewhere).

Reports which exclusively focused on the treatment of patients with bipolar disorder, dysthymic disorder, minor depressive disorder seasonal affective disrder, or for depressed patients with a specific medical condition as well as reports containing patients with psychotic features or patients with active alcohol or substance abuse disorders were excluded from the analysis.

2.3. Data extraction

Data were extracted with the use of a pre-coded form. The following data were extracted from studies which met criteria for inclusion in the meta-analysis: the criteria used to establish the diagnosis of MDD, the number of patients randomized to each treatment arm, the antidepressants and doses used, the duration of the trial, the primary outcome measure used (HDRS, MADRS or CGI), response rates, overall discontinuation rates, the rate of discontinuation due to adverse events, and the rate of discontinuation due to inefficacy.

2.4. Quantitative data synthesis

The primary outcome of the meta-analysis was to compare response rates between the 5HT2 antagonist- and SSRI-treated groups. To accomplish this, we pooled the estimates of response rates among studies after examining for homogeneity using the test statistic proposed by DerSimonian and Laird [8]. Examination of the pooled results was performed using both the fixed and random effects models to ascertain differences in pooled estimates by the two techniques [8,19,22]. We presented as our final estimate the findings of the random effects model; this model is more conservative than the fixed-effects model and incorporates both within-study and between-study variance. Finally, we performed an examination for publication bias using a funnel plot and Eggers test statistic [34]. Secondary outcomes included comparing overall discontinuation rates, the rate of discontinuation due to adverse events, and the rate of discontinuation due to inefficacy. We also used a random effects model to compare the 5HT2 antagonist- and SSRI-treated groups on all secondary outcome measures. All analyses utilized the meta package of meta-analytic tools as implemented in Stata 8.0 (College Station, TX).

3. Results

Initially 716 abstracts were identified. Of these, 700 did not meet the inclusion criteria (other topics, reviews). The articles pertaining to the remaining 16 abstracts were obtained, and reviewed thoroughly. Five of these articles [2,7,12,13,31] described studies published elsewhere in greater detail ([7,12,31] in [5]; [2,13] in [33]). One article was excluded because it described an open-label trial [3], and one because it involved randomizing sertraline responders with sexual side-effects to either continue with sertraline or undergo a switch to nefazodone [11]. The 9 remaining articles ($n = 988$) described studies meeting criteria for inclusion in the meta-analysis (Table 1). None of the studies pooled involved the use of a placebo-control group. Seven of 9 studies were funded by the makers of either nefazodone (Bristol Myers Squibb), or trazodone PR (Angelini SpA). The remaining two studies involved a comparison between trazodone and fluoxetine, and were funded by the makers of fluoxetine (Eli Lilly).

3.1. Analysis of primary and secondary outcome measures

There was no statistically significant difference in response rates between the 5HT2-receptor antagonist- and SSRI-treated groups. Specifically, across the trials, the pooled risk ratio (RR) for response was 1.002 (95% CI: 0.85–1.17, $P = 0.978$) for the random effects model. Simply pooling response rates between the two agents revealed a 61.1% response rate for the 5HT2-receptor antagonists, and a 61.7% response rate for the SSRIs (Fig. 1). A test for heterogeneity suggested no significant heterogeneity between the included studies ($Q = 5.774$; 8 df; $P = 0.676$). The Eggers test was not suggestive for the presence of publication bias

Table 1
Studies included in the meta-analysis

Study	Efficacy measure	5HT2 antagonist	5HT2 dose	SSRI	SSRI dose	Duration (weeks)	Sponsor
Falk et al., 1989 [9]	HDRS	Trazodone	50–400	Fluoxetine	20–60	6	Eli Lilly
Beasley et al., 1991 [5]	HDRS	Trazodone	50–400	Fluoxetine	20–60	6	Eli Lilly
Baldwin et al., 1996 [4]	CGI-I	Nefazodone	200–600	Paroxetine	20–40	8	BMS
Feiger et al., 1996 [10]	HDRS	Nefazodone	100–600	Sertraline	50–200	6	BMS
Berlanga et al., 1997 [6]	CGI-I	Nefazodone	200–500	Fluoxetine	20–40	8	BMS
Rush et al., 1998 [33]	HDRS	Nefazodone	200–500	Fluoxetine	20–40	8	BMS
Hicks et al., 2002 [16]	HDRS	Nefazodone	400–600	Paroxetine	20–40	8	BMS
Kasper et al., 2005 [18]	HDRS	Trazodone PR	300–450	Paroxetine	20–40	6	Angelini SpA
Munizza et al., 2006 [23]	HDRS	Trazodone PR	150–450	Sertraline	50–100	6	Angelini SpA

5HT2, serotonin-2 receptor; SSRI, selective serotonin reuptake inhibitor; HDRS, Hamilton Depression Rating Scale; CGI, Clinical Global Impressions/Improvement Scale; BMS, Bristol Myers Squibb; PR, prolonged release.

($P = 0.100$). Visual inspection of the funnel plot was also not suggestive of publication bias (Funnel plot not shown). There was also no difference in overall discontinuation rates (RR = 0.87; 95% CI: 0.65–1.15; $P = 0.334$), the rate of discontinuation due to adverse events (RR = 0.9; 95% CI: 0.72–1.14; $P = 0.676$), or the rate of discontinuation due to inefficacy (RR = 0.69; 95% CI: 0.35–1.36; $P = 0.289$) between the two groups.

4. Discussion

In the present meta-analysis, we found no evidence suggesting a difference in response rates when comparing the 5HT2-receptor antagonists trazodone or nefazodone with the SSRIs for the treatment of MDD. Specifically, the likelihood of patients experiencing significant clinical improvement during treatment was comparable for both agents. Simply pooling response rates between the two agents revealed a 61.1% response rate for the 5HT2-receptor antagonists and a 61.7% response rate for the SSRIs. A similar proportion of trazodone/nefazodone and SSRI-treated patients discontinued treatment for any reason, or specifically due to lack of clinical improvement or side-effects. These results are in accordance with several other meta-analyses which suggesting no difference in overall efficacy when comparing the SSRIs with other antidepressants or antidepressant classes [1,17,24,26,28,29,30,35]. However, confirmation that trazodone/nefazodone and the SSRIs are comparably effective in terms of the likelihood of response at the end of acute phase therapy does not mean that the drugs are equally useful for particular depressed patients. Indeed, given the heterogeneity of major depressive disorder and the relative advantage of all antidepressants over placebo in clinical trials [27], it is possible that subgroups of patients are more responsive to one or the other type of antidepressant.

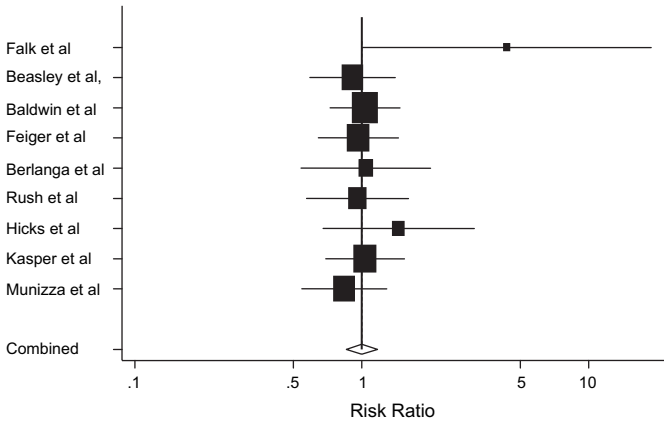

Fig. 1. Primary meta-analytical findings.

We note several important limitations of our work. First, the analysis involved pooling studies comparing either trazodone or nefazodone with fluoxetine, sertraline, and paroxetine. Since studies involving citalopram, escitalopram and fluvoxamine were not included, conclusions drawn from this study cannot be generalized to these latter three SSRIs. Another significant limitation of our analysis is related to the fact that none of the included studies had a placebo comparison group. Therefore, one cannot draw any conclusion about the "assay sensitivity" of these trials, whose response rates may have been confounded by robust, non-specific, placebo-like effects. An additional limitation is that the present work involved pooling clinical trials, which involve a number of inclusion and exclusion criteria. Hence, it may not be possible to directly extend the findings of this study to groups of patients typically excluded from participating in randomized clinical trials. Furthermore, pooled analyses and meta-analyses involve combining studies of heterogeneous design. In general, a single clinical trial of equivalent sample size can yield more accurate estimates of a treatment effect. However, for the most part, the trials pooled in the present analysis had many similarities, including a 1-week washout period prior to randomization, a comparable baseline depression severity threshold for inclusion, and similar treatment duration. Other limitations specifically pertain to the identification of studies to be included in pooled analyses or meta-analyses, and include the phenomenon of publication bias. Thus, although we included all published studies, it is quite possible that other studies may have been conducted but have not been published as of yet. However, in our analysis there was no statistical evidence suggesting the presence of publication bias. Finally, all studies included in the analysis were of 6–8 weeks in duration. Whether the present findings would extend beyond the acute phase of treatment remains to be determined.

5. Conclusion

These results suggest that the 5HT2-receptor antagonists trazodone and nefazodone and the SSRIs do not differ with respect to their overall efficacy in the treatment of MDD. It should be noted that although the sample size was relatively large and conveyed sufficient statistical power to test for differences in the overall sample, depression is a heterogeneous condition and differences may exist between treatments in particular subgroups of patients.

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