Pindolol augmentation of selective serotonin reuptake inhibitors and clomipramine for the treatment of obsessive-compulsive disorder: A meta-analysis

Sir,

Obsessive-compulsive disorder (OCD) is associated with an estimated lifetime prevalence of 2%.[1] An estimated 50–80% of the patients are treatment-resistant, with either no response or a limited response to adequate trials of selective serotonin reuptake inhibitors (SSRIs) and clomipramine.[1] The American Psychiatric Association (APA) Practice Guidelines recommend augmentation with atypical antipsychotics, an alternate SSRI, mirtazapine, or venlafaxine as second-line treatment options. The use of pindolol is currently considered as a third-line augmentation strategy for patients with inadequate response to the aforementioned treatment options.[1]

Pindolol exerts antihypertensive effects through β-blockade, and is also a potent serotonin $5HT_{1A}$ presynaptic receptor antagonist. The serotonin $5HT_{1A}$ receptor is primarily an autoreceptor, and agonism of this receptor downregulates serotonin release. Pindolol augmentation theoretically leads to an increased release of serotonin through the blockade of the $5HT_{1A}$ receptor.[2]

The APA guidelines note that limited evidence exists to support the use of pindolol as an augmentation strategy, and a meta-analytic review would aid in the evaluation of the current evidence for its use. A meta-analysis is particularly useful in situations where few studies have been performed, especially when those studies have employed small sample sizes. In these situations, a meta-analysis can provide an overall measure of medication efficacy that would be otherwise unavailable, owing to low statistical power. To date, no systematic review or meta-analysis of the literature examining the efficacy of pindolol augmentation has been performed. The purpose of this study was to determine the level of evidence supporting pindolol augmentation of SSRIs and clomipramine for the treatment of OCD, by performing a quantitative review of the literature through the use of meta-analytic techniques.

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRIMSA)[3] guidelines were followed. Ovid Medline, PubMed, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, and review of article references were used to search for all studies examining pindolol augmentation for the treatment of OCD. The search terms included pindolol, beta-blocker, serotonin $5HT_{1A}$, and obsessive-compulsive disorder. To maximize the statistical power, all studies that were published in peer-reviewed journals prior to June 30, 2014, were included, regardless of the study design or language of publication. The Yale–Brown Obsessive-Compulsive Scale is the most commonly used measure of OCD severity, and was used as the measure of efficacy in the meta-analysis. The standard meta-analytic techniques were employed for data extraction.[4] Calculations were performed manually, with the use of the Statistical Package for Social Sciences,[5] as a second point of reference. The Pearson correlation coefficient *r* was used as the effect size measure, given that it was applicable to statistical analyses of repeated measures. Cohen's *d* is also commonly used in meta-analytical research, and is easily calculated from *r*, but is not readily interpretable in repeated

Table 1: Descriptive data and associated effect sizes of the study

Author	Year	*n*	*r*	Mean (SD)		Study design	Pindolol dose	Additional concurrent therapy
				Age	YBOCS total decrease			
Blier *et al.*	1996	13	0.35	33.90 (9.81)	3.00 (4.00)	Single sample, longitudinal	2.5 mg to 5 mg p.o b.i.d	Clomipramine (*n*=1) Fluoxetine (*n*=4) Fluvoxamine (*n*=1) Paroxetine (*n*=7)
Koran *et al.*	1996	8	0.35	36.57 (12.71)	3.28 (8.69)	Single sample, longitudinal	2.5 mg p.o q.a.m and 5 mg p.o q.h.s or 5 mg p.o b.i.d	Clomipramine (*n*=4) Fluoxetine (*n*=1) Sertraline (*n*=2)
Dannon *et al.*	2000	14	0.65	34.84 (11.84)	5.00 (3.14)	Double-blind RCT	2.5 mg p.o t.i.d	Paroxetine (*n*=16)
Mundo *et al.*	1998	15	0.00	28.80 (2.64)	0.00[a]	Double-blind RCT	2.5 mg p.o t.i.d	Fluvoxamine (*n*=15) Previously established doses of benzodiazepines (*n* not presented)

[a]Insufficient information provided to calculate SD, YBOCS=Yale-Brown obsessive-compulsive scale, RCT=Randomized controlled trial, SD=Standard deviation

measure designs. A full discussion on effect size indices was beyond the scope of this article, and the interested reader has been referred elsewhere for more information.[4] Data were independently reviewed by the authors, with complete agreement on the efficacy prior to inclusion in the data set. Analyses were performed using a random effects model, in which studies were considered as the sampling unit, and a fixed effects model, where individual patients in the studies were considered as the sampling unit.

Four published studies (N = 50) that investigated the effect of pindolol augmentation were identified and included in the meta-analysis.[6-9] Descriptive data and effect size estimates for reductions in OCD symptoms for the studies are presented in Table 1. Greater values of r indicate greater efficacy of pindolol.

Pindolol augmentation of SSRIs and clomipramine significantly reduced OCD symptoms in the random ($t_{(3)}$ = 2.39, r = 0.36, $p_{\text{one-tailed}}$ = 0.048, *95%* CI = 0.067–0.59) and fixed effects models (k = 4, N = 50, z = 3.18, r = 0.35, $p_{\text{one-tailed}}$ = 0.00075, *95%* CI = 0.046-0.59). Fail-safe N analysis found the number of new or unretrieved studies averaging nil results, which were required to bring the overall $p_{\text{one-tailed}}$ to 0.05, to be N = 8.

When only the randomized placebo-controlled trials were analyzed,[8,9] pindolol augmentation was associated with a non-statistically significant trend toward reduction of OCD symptoms in the random ($t_{(1)}$ = 1.00, r = 0.37, $p_{\text{one-tailed}}$ = 0.25, *95%* CI = –0.60 – 0.90) and fixed effect models (k = 2, N = 29, z = 0.88, r = 0.18, $p_{\text{one-tailed}}$ = 0.19, *95%* CI = –0.23 – 0.54).

Three of the studies reported that no significant adverse effects of pindolol were experienced by patients.[6,8,9] The fourth study[7] included in the meta-analysis did not report whether adverse effects were experienced. From the preliminary evidence, it appears that pindolol is a safe treatment option, when used at doses included in the current studies.

Pindolol was ineffective in one randomized controlled trial, which was also the single study that simultaneously initiated pindolol and fluvoxamine.[9] A potential explanation for this finding involves the competing pharmacological mechanisms of these two medications. Fluvoxamine is theorized to act as an indirect agonist at $5HT_{1A}$ receptors through increases in serotonin, which results from inhibition of the serotonin reuptake pump. Pindolol, however, is a potent antagonist at the $5HT_{1A}$ receptor. This suggests that it may be beneficial to delay therapy with pindolol until the maximum benefit of the initial serotonergic antiobsessional agent has been achieved. However, more research is needed.

The main limitation of this meta-analysis is the small number of studies included, only two of which were randomized controlled trials. However, the major benefit of meta-analytic research is the combination of the results of small studies to calculate the measure of efficacy that would otherwise be unavailable. This meta-analysis provides clinicians with the best available assessment of the utility of pindolol as an augmentation strategy for the treatment of OCD. Medium effect sizes, defined as r = 0.3, were found for the efficacy of pindolol, including in the analysis of solely randomized controlled trials. Although publication bias toward positive results is possible, the fail-safe N of eight studies indicates some tolerance for the unpublished negative studies.

The authors hope the results of this meta-analysis will lead to increased research examining the use of pindolol for OCD, a mental disorder in need of effective treatment options. Although further study is needed to fully characterize the efficacy of pindolol for the treatment of OCD, preliminary evidence suggests that pindolol may be a useful adjunctive medication.

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