**Time to reconsider monoamine oxidase inhibitors (MAOIs) for Obsessive Compulsive Disorder? A case series using phenelzine**

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**Abstract**

Purpose/Background: Despite the availability of a range of efficacious evidence-based treatments for Obsessive-Compulsive Disorder (OCD), not all patients experience sufficient benefit or are able to tolerate them in practice. Monoamine oxidase inhibitors (MAOIs) show efficacy in the treatment of depression and certain anxiety disorders (such as social anxiety disorder).

Methods/Procedures: We survey the evidence base from case reports, and clinical trials, regarding use of MAOIs in OCD. We then present new data from a case series collected in routine clinical practice in a specialist clinical service.

Findings/Results: In nine treatment-resistant patients whose OCD had not improved with at least two standard treatment trials, three had marked clinical improvement (>35% improvement on YBOCS) on phenelzine, three had some improvement (15-34.9%), and three showed minimal or no improvement (<15%). In the three patients who experienced minimal/no improvement, two had discontinued early due to lack of tolerability, and the other patient discontinued after four weeks due to perceived lack of symptom benefit.

Implications/Conclusions: We suggest that (1) MAOIs in treatment-resistant OCD require appropriate research scrutiny in large-scale randomised controlled trials; and (2) MAOIs merit consideration as a treatment option in individual cases of OCD, particularly in specialist settings where first-line interventions have proven inadequate to manage severe symptoms.

**Introduction**

Obsessive-Compulsive Disorder (OCD) is characterized by repetitive intrusive thoughts (obsessions) and/or repetitive rituals undertaken in response to those thoughts, or according to rigid rules. OCD is a common mental health disorder (lifetime prevalence rate of approximately 1.5%) (1) and is often accompanied by increased anxiety, depression, and other psychosocial dysfunction (2). Current first-line treatments include cognitive behavioral therapy using exposure response prevention and/or serotonin reuptake inhibitors (SRIs) (including both selective serotonin reuptake inhibitors [SSRIs] and the tricyclic medication clomipramine) (3). While helpful for many patients, up to 35% of people do not experience adequate symptom relief from these interventions (2), and not all individuals are able to tolerate them. Thus, other options are needed.

Monoamine oxidase inhibitors (MAOIs) show efficacy in other conditions such as depression, and anxiety disorders such as social anxiety disorder, but are often overlooked in clinical practice. In a recent position statement by the Royal College of Psychiatrists, attention was drawn to the need to consider MAOIs as potential treatment options for these other conditions. As the SRIs are not effective in everyone with OCD, are the monoamine oxidase inhibitors (MAOIs) worth consideration?

In terms of previous reports and case series, in one of the first cases of pharmacological treatment for OCD, Ainsley describes a patient with refractory OCD (status-post leucotomy) who remitted after 6 weeks of phenelzine 60mg/d (4). This was followed by a report from Jain and colleagues describing a young man with severe OCD who had failed to respond to neuroleptics and a tricyclic antidepressant only to have substantial improvement when switched to phenelzine 45mg/d (5). Several years later, Isberg compared imipramine to phenelzine on a single patient and found that whereas imipramine (500mg/d) was ineffective for the contamination obsessions, 75mg of phenelzine was associated with near remission within 2 weeks (6). Jenike and colleagues reported 8 patients taking phenelzine for OCD of whom 4 responded, and each of the responders had had co-occurring phobic anxiety and/or panic attacks (none of the 4 non-responders had this comorbidity) (7). Further support was found in a case report by Mahgoub in 1987 wherein he described a patient who after failing clomipramine and ECT had a trial of phenelzine at 90mg/d and had a robust response after 7 weeks, followed by almost immediate relapse upon stopping phenelzine (8).

Only a few clinical trials have been conducted using MAOIs in OCD. In a double-blind randomised cross-over trial in patients with DSM-III defined OCD, clomipramine appeared beneficial whereas the MAOI clorgyline was not associated with significant improvement (in the whole group, though some individuals fared well) (9). In 1992, a double-blind trial of clomipramine versus phenelzine was published. The study enrolled 30 patients with OCD who were treated for 12 weeks with either 225 mg/day of clomipramine (14 patients) or 75 mg/day of phenelzine (12 patients) (4 patients dropped out). Obsessive symptoms improved significantly in both drug groups, with no significant difference between groups (10). Another double-blind study compared placebo, phenelzine (60 mg/day), or fluoxetine (80 mg/day) in 54 adults with OCD (11). The treatment arms differed overall in YBOCS changes, but not on other outcome measures: YBOCS scores in the fluoxetine group were significantly lower than placebo at weeks 6 and 10, and were lower than phenelzine at week 10. However, it is difficult to know what to make of these results for several reasons. The treatment arms did not differ overall on other OCD severity outcome measures, and absolute mean changes using the YBOCS were relatively small: average scores being 18-19 at baseline to 16-19 at study endpoint. So even if statistically different, the response to fluoxetine was from 19.0 to 16.2 on the YBOCS, compared to 18.0 to 16.3 for phenelzine.

Given these data, one wonders why MAOIs have not been pursued more in the treatment of OCD, particularly given controlled comparator studies in which they have demonstrated benefit either equal or slightly inferior (when dose limited to 60 mg of phenelzine) to clomipramine or an SSRI. This may in part be due to the risk burden of an MAOI and the lack of evidence of superiority at a group level. Thus, although MAOIs may not be an ideal first-line option for OCD, do they have a potential role in patients with treatment-resistant OCD? Clinically, it is important to note the important safety considerations when commencing MAOI, including the need for a suitably appropriate washout period after discontinuing previous SRI medication.

These prior studies of MAOIs for OCD did not enroll treatment-resistant patients (except for individual case reports) and thus the efficacy of MAOIs in these patients is unclear. The aim of the current study therefore was to examine the treatment response and tolerance of the irreversible MAOI phenelzine in adults with treatment-resistant OCD. We focused on phenelzine in light of the above, and network meta-analytic evidence suggesting it may be more effective than other treatments (including non-MAOIs) for depressive disorders (12). This was a chart review of all patients with treatment-resistant OCD started on phenelzine within the last two years to examine who responded and at what dose and for how long. We hypothesized that phenelzine would potentially be associated with marked symptomatic improvement in some of these patients.

**Materials and Methods**

Records from nine consecutive adult outpatients with DSM-5-defined OCD as their primary diagnosis who had sought treatment voluntarily in a specialty clinic for OCD were evaluated to assess outcome of phenelzine. Only patients receiving phenelzine, as monotherapy or in combination with other medications, were included in the chart review. Patients electing to receive psychotherapy, either alone or in combination with medication, were also included in this analysis. However, this was only permitted if the other treatment(s) had been underway for at least 3 months and continued unchanged during phenelzine treatment.

Baseline information included current age, comorbid diagnoses, and OCD symptom severity assessment using the *Yale Brown Obsessive Compulsive Scale (YBOCS)* (13) as part of routine clinical practice. Total YBOCS scores constituted the *a priori* primary outcome measure. For clinical purposes of examining symptom severity and change over time, patients were rated at each visit using the YBOCS.

In general, patients were started on phenelzine 15 mg twice daily and after one week were increased to 30mg twice daily and then to 45mg twice daily one week later, if tolerated.

The institutional review board of the University of Chicago approved the chart review. As part of routine clinical care, patients were informed of the off-label use of phenelzine. All patients provided informed written consent for treatment and for their anonymized data to be used. The authors assert that all procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

**Results**

 **Table 1** shows an overview of the patients in the case series, and salient information. The dose of phenelzine for the nine patients ranged from a total of 45-90mg per day (typically in two divided doses), and the duration of phenelzine treatment was 2 weeks to > 8 months (i.e. patients who continued it longer term, beyond the initial follow-up period). Shorter durations were due to lack of tolerability.

 Across the pooled sample, total YBOCS scores while on phenelzine decreased by an average of 6.8 points (standard deviation 5.0 points), this representing an average improvement versus baseline of 23.9% (baseline refers to when patients were typically on long-term other medications that had yielded limited benefit). Of the nine patients, three improved more than 35% on the YBOCS, three improved 15%-34.9%, and three showed minimal or no improvement (<15%). Of the three patients with minimal/no improvement, two discontinued early due to intolerability (in both cases the patients reported orthostatic hypotension), and one person discontinued after 4 weeks of treatment due to limited perceived symptomatic benefit. Other than the two patients who reports intolerable orthostatic hypotension, the other seven patients reported the following side effects, all of which were reported as mild: 5 reported dry mouth; 3 reported transient nausea/diarrhea; 3 had delayed orgasm; and 1 reported weight gain of approximately 10 pounds.

**Discussion**

 This case series shows that in patients treated in a specialist OCD clinic, phenelzine was associated with notable symptom improvements in some patients (6 of 9) who had previously not experienced benefit from other more usual treatments. The three patients who did not experience any symptom benefit either discontinued treatment due to intolerability, or stopped after 4 weeks due to lack of symptom improvement.

 Somewhat consistent with the previous report by Jenike and colleagues (7), in which benefit with MAOIs in OCD occurred in patients with phobias or panic attacks, in this report we found that the three patients with the least improvement (as well as the 21-year-old male, who had a 23% improvement) did not have a comorbid anxiety disorder. Thus, it begs the question as to whether "pure" OCD may be less likely to respond to MAOIs than OCD that is comorbid with depression or anxiety.

Of course, case reports as presented here have inherent limitations due to the lack of blinding and control conditions. However, we would highlight that these patients had treatment resistant OCD symptoms that persisted despite rigorous use of more typical interventions. Although the passage of time or the placebo effect could be possible explanations for improvement, it seems more likely that the observed clinical improvements during phenelzine treatment were due to the medication itself.

In conclusion, MAOIs are being highlighted as important treatment options in other areas of mental health such as depression and anxiety disorders besides OCD. In a recent network meta-analysis, phenelzine demonstrated superior efficacy compared to other treatments in depressive disorders (12). The current case series highlight the urgent need to properly evaluate MAOIs in relation to treatment of OCD, ideally in large appropriately powered high-quality randomized controlled trials. We suggest MAOIs merit consideration as a treatment option for OCD, especially in treatment-resistant cases, with appropriate discussion of benefits and risks, including the need to consider drug interactions and dietary restrictions.

**References**

1. Fawcett EJ, Power H, Fawcett JM. Women Are at Greater Risk of OCD Than Men: A Meta-Analytic Review of OCD Prevalence Worldwide. J Clin Psychiatry. 2020 81:19r13085.
2. Grant JE. Clinical practice: Obsessive-compulsive disorder. N Engl J Med. 2014 371:646-653. doi: 10.1056/NEJMcp1402176. PMID: 25119610.
3. Skapinakis P, Caldwell D, Hollingworth W, et al. A systematic review of the clinical effectiveness and cost-effectiveness of pharmacological and psychological interventions for the management of obsessive-compulsive disorder in children/adolescents and adults. Health Technol Assess. 2016 20:1-392. doi: 10.3310/hta20430. PMID: 27306503; PMCID: PMC4921795.
4. Annesley PT. Nardil response in a chronic obsessive compulsive. Br J Psychiatry. 1969 115:748. doi: 10.1192/bjp.115.523.748. PMID: 5806868.
5. Jain VK, Swinson RP, Thomas JG. Phenelzine in obsessional neurosis. Br J Psychiatry. 1970 117:237-238. PMID: 5480680.
6. Isberg RS. A comparison of phenelzine and imipramine in an obsessive-compulsive patient. Am J Psychiatry. 1981 138:1250-1251. doi: 10.1176/ajp.138.9.1250. PMID: 7270738.
7. Jenike MA, Surman OS, Cassem NH, et al. Monoamine oxidase inhibitors in obsessive-compulsive disorder. J Clin Psychiatry. 1983 44:131-132. PMID: 6833198.
8. Mahgoub OM. A remarkable response of chronic severe obsessive-compulsive neurosis to phenelzine. Acta Psychiatr Scand. 1987 75:222-223. doi: 10.1111/j.1600-0447.1987.tb02779.x. PMID: 3565070.
9. Insel TR, Murphy DL, Cohen RM, et al. Obsessive-compulsive disorder. A double-blind trial of clomipramine and clorgyline. Arch Gen Psychiatry. 1983 40:605-612.
10. Vallejo J, Olivares J, Marcos T, et al. Clomipramine versus phenelzine in obsessive-compulsive disorder. A controlled clinical trial. Br J Psychiatry. 1992 161:665-670. doi: 10.1192/bjp.161.5.665. PMID: 1422616.
11. Jenike MA, Baer L, Minichiello WE, et al. Placebo-controlled trial of fluoxetine and phenelzine for obsessive-compulsive disorder. Am J Psychiatry. 1997 154:1261-1264. doi: 10.1176/ajp.154.9.1261. PMID: 9286186.
12. Suchting R, Tirumalajaru V, Gareeb R, et al. Revisiting monoamine oxidase inhibitors for the treatment of depressive disorders: A systematic review and network meta-analysis. J Affect Disord. 2021 282:1153-1160.
13. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch Gen Psychiatry. 1989 46:1006-1011. doi: 10.1001/archpsyc.1989.01810110048007.

**Table 1. Demographic and clinical characteristics of the cases.**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Age** | **Gender** | **Comorbidities** | **Medication prior to phenelzine** | **YBOCS 1\*** | **Phenelzine dose (mg)** | **Phenelzine duration** | **Side effect (s)** | **YBOCS 2\*\*** |  | **Improvement?** |
| 26 | Male | Social anxiety disorder | Sertraline 200 mg; citalopram 40 mg; memantine 20 mg | 26 | 90 | 8 months + | Dry mouth; transient nausea/diarrhoea | 22 |  | + |
| 35 | Male | None | Sertraline 200 mg; fluoxetine 100 mg; fluvoxamine 300 mg; clomipramine 250 mg | 27 | 45 # | 6 weeks | Orthostatic hypertension | 27 |  | - |
| 26 | Female | Depression | Sertraline 300 mg; escitalopram 30 mg; aripiprazole 15 mg; risperidone 1 mg; clomipramine 250 mg | 29 | 90 | 16 months | Dry mouth | 16 |  | ++ |
| 33 | Male | Generalised anxiety disorder | Fluoxetine 80 mg; aripiprazole 5 mg; clomipramine 200 mg | 24 | 90 | 6 months | Transient nausea/diarrhoea | 12 |  | ++ |
| 37 | Female | None | Fluoxetine 80 mg; escitalopram 30 mg; clonazepam 1 mg; clomipramine 100 mg | 32 | 60 # | 4 weeks |  | 30 |  | - |
| 21 | Male | None | Fluoxetine 80 mg; escitalopram 30 mg; paroxetine 40 mg; risperidone 2 mg; memantine 10 mg | 30 | 90 | 10 months | Dry mouth; transient nausea/diarrhoea; delayed orgasm | 23 |  | + |
| 43 | Female | Depression | Fluoxetine 80 mg; citalopram 40 mg; ; fluvoxamine 300 mg; clomipramine 50 mg | 33 | 45 # | 2 weeks | Orthostatic hypertension | 31 |  | - |
| 34 | Female | Social anxiety disorder | Fluoxetine 80 mg; escitalopram 40 mg; aripiprazole 10 mg; memantine 10 mg; clomipramine 150 mg | 32 | 90 | 8 months + | Dry mouth; delayed orgasm; weight gain approx. 10 pounds | 27 |  | + |
| 51 | Male | Depression; Generalised anxiety disorder | Fluoxetine 80 mg; escitalopram 30 mg; buspirone 60 mg; risperidone 2 mg; clonazepam 1mg | 30 | 90 | 14 months | Dry mouth; delayed orgasm | 14 |  | ++ |

**\*:** Prior to phenelzine (while on medications to the left); **\*\*:** After phenelzine.

++: >35% improvement on YBOCS on phenelzine; +: 15-34.9% improvement; -: <15% improvement.

# Indicates receiving regular (stable) CBT treatment prior to and during phenelzine treatment.