Treating Depression With Atypical Features

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Depression with atypical features was first recognized in a subset of patients with depression who preferentially responded to the monoamine oxidase inhibitor (MAOI) phenelzine, in contrast to patients with melancholic depression. This article reviews the history of approaches in treating depression with atypical features. Initial studies in the early 1980s focused on phenelzine, but an unfavorable adverse effect profile limits its clinical use. Despite such difficulties, phenelzine remains the gold standard in eliciting high response rates in nearly two thirds of patients with atypical depression. Searches for agents with improved safety profiles led to studies of tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), chromium, and cognitive therapy approaches. Of these, TCAs showed inferior efficacy to MAOIs but also had cumbersome adverse effects. SSRIs have reported efficacy, but a lack of direct comparative studies limits clinical decision making. Cognitive strategies have shown promise, but demonstrating efficacy in comparison with an MAOI and placebo is limited to a single study. Despite advances in agents for melancholic depression, treatment for atypical depression remains dependent upon older agents for the greatest efficacy.

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The concept of depression with atypical features evolved from the recognition that a subset of patients with depression had characteristics inconsistent with melancholic depression. These patients presented with nonmelancholic features including mood reactivity, hypersomnia, hyperphagia, sensitivity to interpersonal rejection, and leaden paralysis.[1] Patients with these features also responded differently to pharmacologic intervention compared with patients with melancholic depression. Specifically, they were less likely to respond to treatment with tricyclic antidepressants (TCAs) than to a monoamine oxidase inhibitor (MAOI). Several studies were performed to more fully characterize this difference in pharmacologic response. Furthermore, because the use of MAOIs requires strict adherence to dietary rules to avoid serious adverse reactions with certain foods and medications, studies have examined other agents in attempts to identify compounds with similar efficacy as MAOIs but with improved safety profiles.

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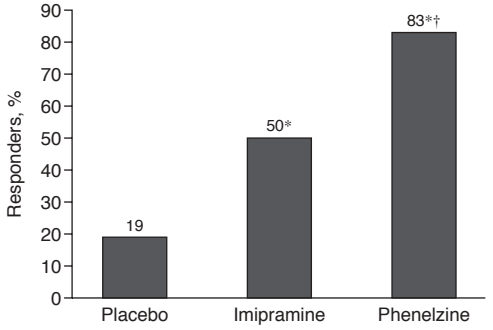
MONOAMINE OXIDASE INHIBITORS VERSUS TRICYCLIC ANTIDEPRESSANTS

Studies published in the late 1980s and early 1990s documented the responsiveness of depression with atypical features to drug treatment. In the largest of these studies,[2] 119 patients with depression, mood reactivity, and 2 other symptoms (overeating, oversleeping, chronic oversensitivity to rejection, or extreme fatigue when depressed) were included and considered to have definite atypical depression. Patients who did not respond to a 10-day course of placebo were randomly assigned to receive the MAOI phenelzine, the TCA imipramine, or placebo. This 6-week, double-blind study reported response rates of 71%, 50%, and 28% for phenelzine, imipramine, and placebo, respectively. Both active drug arms were significantly different from placebo ($p < .05$). Although the difference between active drugs did not reach statistical significance, phenelzine showed a trend for superiority to imipramine. Study authors concluded that the greater efficacy of phenelzine compared with imipramine supported the idea that atypical depression was differentiated from melancholic depression partly by responsiveness to an MAOI. To further test this idea, Quitkin and colleagues[3] performed a study to replicate the initial findings. In this study, 90 patients with probable atypical depression were enrolled and underwent an identical regimen as in the study by Liebowitz and colleagues.[2] At 6 weeks, a significant difference between placebo and active treatment groups had emerged (Figure 1). Further, phenelzine was shown to be significantly superior to imipramine as measured by Clinical Global Impressions scale (CGI),

Figure 1. Efficacy of Phenelzine, Imipramine, and Placebo in Patients With Atypical Depression[a]



[a]Data from Quitkin et al.[3]
*p < .001 vs. placebo.
†p = .005 vs. imipramine.

Hamilton Rating Scale for Depression (HAM-D), and Hopkins Symptom Checklist (SCL-90) scores. When compared with results from the original study, main outcomes were nearly identical.[3]

To further examine the apparent subgroup difference in response to pharmacotherapy, a study[4] of patients with depression and reactive mood without atypical symptoms (i.e., simple mood-reactive depression) was undertaken using an identical design as previously discussed.[2] At 6 weeks, response rates were 25% for placebo, 74% for imipramine, and 75% for phenelzine. Although both active drugs were significantly different from placebo (p = .001), they were nearly identical to one another. While the response rates for placebo and phenelzine across studies were consistent, the simple mood-reactive depression group had a much greater response rate to imipramine than patients with definite atypical depression and probable atypical depression in the other studies. Study authors concluded that the presence of atypical symptoms predicted response to MAOI and TCA treatment. The repeatability of differential drug responsiveness based upon the presence or absence of atypical features argued for the inclusion of atypical features in the DSM-IV criteria.

In a subsequent study[5] using a crossover design, patients with atypical depression who were nonresponsive to 7 weeks of placebo treatment were randomly assigned to treatment with imipramine or phenelzine. After 6 weeks of active drug treatment, patients who responded to treatment continued for another 6 weeks. Response rates at 6 and 12 weeks were 35% and 24%, respectively, for imipramine, and 63% and 51% for phenelzine. The imipramine-phenelzine differences were significant (p < .05). Significant differences favoring phenelzine were also reported for CGI and HAM-D scores and on some items of the SCL-90 instrument. These results again supported the existence of a distinct subgroup of depression and preferential responsiveness of atypical depression to MAOI therapy. A second crossover study[6] described outcomes for patients from the previous randomized studies who were unresponsive to the first active treatment drug and were switched under blinded conditions to the second active drug (N = 89). Of those completing the crossover study, 67% of patients unresponsive to imipramine responded to phenelzine, whereas 41% of patients unresponsive to phenelzine responded to imipramine. Although the treatment groups cannot be directly compared, the study again underscored the greater efficacy of MAOIs in treating atypical depression.

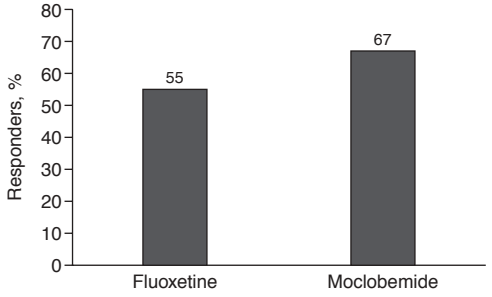
MONOAMINE OXIDASE INHIBITORS VERSUS NON–TRICYCLIC ANTIDEPRESSANT TREATMENTS

Additional studies have compared the efficacy of MAOIs with non-TCA approaches to therapy. These include comparisons with selective serotonin reuptake inhibitors (SSRIs) and cognitive-behavioral therapy (CBT). In addition, the utility of selegiline, a drug specifically inhibiting monoamine oxidase B at low doses, was studied[7] as a possible method to avoid the risk of hypertensive crisis associated with monoamine oxidase A inhibition. Patients unresponsive to 10 days of placebo were randomly assigned to selegiline (N = 34) or placebo (N = 64). The response rate in patients with atypical depression was 50% and 28% for selegiline and placebo, respectively (p < .05). Twelve percent and 22% of patients in the selegiline and placebo arms, respectively, discontinued from the study. The low occurrence of adverse events suggested that a suboptimal dose may have been used in the study. A suboptimal dose may also explain the lower response rate of this MAOI compared with previous studies of phenelzine. Thus, although selegiline appeared promising, further study using both an adequate dose and a comparison against phenelzine is warranted.

Selective Serotonin Reuptake Inhibitors

Pande and colleagues[8] compared fluoxetine with phenelzine in patients with atypical depression. As in previous studies, this investigation also entailed a placebo run-in period to exclude placebo-responsive patients. Patients continuing in the study received fluoxetine, 20 mg/day titrated to 60 mg/day, or phenelzine, 15 mg/day, increased to a maximum of 90 mg/day for 6 weeks. At study end, response rates for fluoxetine and phenelzine were 80% and 85%, respectively, based on the 17-item HAM-D, and 85% for both groups based on the CGI-Improvement scale (CGI-I). Remission rates were 80% for fluoxetine and 70% for phenelzine. These differences were not significant. Significant differences in treatment-emergent adverse events were reported for dizziness, somnolence, asthenia, and arthralgia, which were more prominent with phenelzine, and tremor, which was more prominent with fluoxetine. The adverse event of confusion led to 1 phenelzine-treated

Figure 2. Relative Efficacy of Fluoxetine and Moclobemide in Patients With Atypical Depression[a]



[a]Data from Lonnqvist et al.[9]

patient's discontinuation. Phenelzine was associated with significant deviations from baseline in supine systolic blood pressure and heart rate and standing diastolic blood pressure. Fluoxetine was associated with significant changes from baseline in body weight. However, the only significant between-treatment difference was for increased supine systolic blood pressure ($p = .004$). On the basis of these results, study authors concluded that fluoxetine and phenelzine were similarly efficacious but that fluoxetine had an improved safety profile. They suggested that fluoxetine was suitable for first-line therapy for patients with atypical depression. However, the small study number ($N = 40$) necessitates replication in a larger trial to determine whether treatment efficacy is truly equivalent or if the study was simply underpowered to detect differences. Future studies should also include a randomized placebo group in order to determine effect size.

A 6-week study[9] of the reversible MAOI moclobemide versus fluoxetine compared the relative efficacies of these agents in depressed patients with and without atypical features. Fifty-three patients with atypical depression and 156 patients with other depression were randomly assigned to moclobemide or fluoxetine. The mean dose for moclobemide was 379 mg for the atypical group ($N = 24$) and 362 mg for the other depression group ($N = 78$). The mean dose for fluoxetine was 27 mg for the atypical group ($N = 29$) and 29 mg for the other depression group ($N = 78$). Efficacy between drugs was similar in the other depression groups. In patients with atypical depression, scores on the Montgomery-Åsberg Depression Rating Scale (MADRS) were significantly better with moclobemide than with fluoxetine ($p < .05$), but no significant difference was reported on the HAM-D. Response rates for patients with atypical depression were 71% and 60% for moclobemide and fluoxetine, respectively, as defined by a decrease of ≥ 50% in HAM-D score, and 91% and 65% ($p < .05$) based on a CGI-I score ≤ 2. When both of these criteria were combined, the response rates were not statistically different (Figure 2). Adverse events were reported by 87% and 61% of patients with atypical and other depression, respectively ($p < .001$), with no difference between treatment arms. Discontinuations occurred in 31% and 13% of fluoxetine- and moclobemide-treated patients with atypical depression ($p < .05$). Although study authors suggested that moclobemide produced a better clinical response, data interpretation is limited because of the lack of a placebo group, the lack of a treatment arm with the well-characterized phenelzine response, the small study number, and the low dose of moclobemide used.

A 12-week study[10] of moclobemide versus the SSRI sertraline for the treatment of atypical depression included a 1-week placebo-washout period prior to randomization to moclobemide ($N = 97$) or sertraline ($N = 100$). Moclobemide was initiated at 300 mg/day with eventual titration to a possible maximum dose of 450 mg/day, while sertraline was initiated at 50 mg/day with eventual titration to a maximum dose of 100 mg/day. At study end, 67.5% and 77.5% of moclobemide- and sertraline-treated patients, respectively, were considered responders on the CGI-I, and 62.7% and 65.2% of moclobemide- and sertraline-treated patients, respectively, were considered responders on the 29-item HAM-D. No statistically significant differences were noted between groups on primary efficacy outcomes. Withdrawals due to adverse events occurred for 8% of sertraline-treated patients and 4.1% of moclobemide-treated patients. At least 1 treatment-emergent adverse event was reported by 77.0% and 84.5% of sertraline- and moclobemide-treated patients, respectively. Although the study did not report differences between treatment arms, it is limited again by the lack of a placebo arm and the suboptimal dose of moclobemide used.

Cognitive-Behavioral Therapy

Because CBT has been shown to be effective in some patients with depression, a 10-week, double-blind, placebo-controlled study[11] of the efficacy of phenelzine versus CBT was conducted in patients with atypical depression. CBT was conducted according to Beck and colleagues[12] and consisted of twice-weekly individual sessions for 10 weeks. Patients with atypical depression were randomized to CBT ($N = 36$), phenelzine ($N = 36$), or placebo ($N = 36$). At study end, both CBT and phenelzine significantly reduced HAM-D scores compared with placebo ($p < .01$). Response rates defined by a HAM-D-21 score ≤ 9 were 58% for both active treatment arms versus 28% for placebo ($p = .01$). Response rates defined by a CGI score ≤ 2 were 61% for both active treatment arms versus 28% for placebo ($p < .01$). Ninety-two percent of phenelzine and 53% of placebo-treated patients reported marked side effects, with significantly more reports of fatigue, sedation, insomnia, dry mouth, dizziness, or increased appetite in the phenelzine group ($p < .01$). Discontinuations occurred for 14%, 25%, and 64% of patients

assigned to CBT, phenelzine, and placebo, respectively. Study authors reported that CBT for acute-phase treatment of atypical depression may be an effective alternative to the use of MAOIs.

COMPARISON OF NON–MONOAMINE OXIDASE INHIBITOR TREATMENTS FOR ATYPICAL DEPRESSION

A third group of studies for patients with atypical depression are those that did not include an MAOI treatment arm. Thus, comparison to the "gold standard" of phenelzine was precluded. In a 20-week, double-blind study,[13] patients with atypical depression were initially treated with a single-blind placebo, and the nonresponders were then randomly assigned to treatment with fluoxetine (N = 49), imipramine (N = 53), or placebo (N = 52). Fluoxetine treatment was initiated at 20 mg/day and titrated to a maximum dose of 60 mg/day, whereas imipramine was initiated at 50 mg/day and then titrated up to 300 mg/day. Response rates based on CGI-I scores were 51% for fluoxetine, 53% for imipramine, and 23% for placebo. Response rates between active drugs were significantly different from placebo ($p < .007$) but not from one another. Similarly, the active drugs improved outcomes on the HAM-D and SCL-90 compared with placebo but not compared with one another. The discontinuation rate was 14% for fluoxetine, 34% for imipramine, and 23% for placebo. Both fluoxetine and imipramine were associated with higher rates of adverse events compared with placebo, such as nausea, dizziness, and constipation for fluoxetine and dry mouth, dizziness, somnolence, constipation, and nausea for imipramine. Compared with one another, imipramine had higher rates of dry mouth, somnolence, and dizziness, while fluoxetine had higher rates of cough and back pain. The study authors noted that both active treatments produced response rates lower than that for MAOIs, but that fluoxetine was moderately effective and well tolerated compared with imipramine. However, while first-line treatment with fluoxetine was supported, the use of imipramine was suggested for patients suffering from insomnia.

Gepirone, a 5-HT_{1A} receptor partial agonist, has not been approved by the U.S. Food and Drug Administration for the treatment of depression, but it has been studied for atypical depression. In an 8-week, double-blind study,[14] 80 patients with atypical depression participated in a 1-week placebo run-in period, and the nonresponders were randomly assigned to treatment with gepirone (N = 29) or placebo (N = 30). At study end, responder rates for the intent-to-treat population based on CGI scores were significantly different between treatment arms. Twenty-three percent of placebo and 79% of gepirone patients who completed the study were considered responders ($p < .001$). Nine and 12 patients in the placebo and gepirone groups, respectively, discontinued from the study. Significant drug-placebo differences favoring gepirone were seen across efficacy measures, including HAM-D and MADRS total scores ($p < .01$). Adverse events more common in the gepirone group included nausea, dizziness, light-headedness, paresthesias, and asthenia. The study suggested the potential utility of a serotonin-selective partial agonist for the treatment of atypical depression. Authors also noted that the response rate of completers on gepirone was comparable to that reported for phenelzine.

Two studies[15,16] examined the effects of chromium treatment for atypical depression. Because chromium enhances insulin action and there is an association between depression and decreased insulin sensitivity, the utility of chromium in addressing both of these conditions is intriguing. In an 8-week, double-blind, preliminary study[15] in 15 patients with atypical depressive disorder, patients were randomized 2:1 to chromium picolinate or placebo. Chromium was initiated at 400 mg and increased to 600 mg after 2 weeks. Response rates were 70% for chromium versus 0% for placebo ($p = .02$). Similarly, remission rates were 60% for chromium versus 0% for placebo ($p = .04$). A 50% reduction in HAM-D score was evident as early as week 2 in half of the chromium patients compared with one fifth of the placebo patients. Chromium was well tolerated, with insomnia occurring in 2 patients. A second study[16] sought to replicate and expand these findings in a large cohort of patients (N = 110). This 8-week, double-blind study randomized patients in a 2:1 ratio to chromium picolinate (N = 70) or placebo (N = 40) using the same methodology as Davidson et al.[15] At study end, there was no difference in efficacy outcomes between placebo and chromium in patients with atypical depression. Discrepancies between this study and the preliminary study were partially attributed to higher baseline HAM-D scores and a greater placebo response in the second study. The replication study showed significant benefits from baseline for both treatment groups. Post hoc analyses found greater benefit with chromium for specific items of the 29-item HAM-D, including appetite, eating, carbohydrate craving, and diurnal variation of feelings. For example, overeating was resolved in 50% of chromium-treated versus 20% of placebo-treated patients. Since carbohydrate craving may predict insulin resistance, further studies of chromium should examine the relationship between carbohydrate craving and the effects of chromium.

CONCLUSION

Treatments for depression with atypical features have included the irreversible MAOIs phenelzine and selegiline, the reversible MAOI moclobemide, the SSRI fluoxetine, the serotonin-selective partial agonist gepirone, chromium, and CBT. Although direct comparisons cannot be made, reports of efficacy appear to favor

MAOIs, followed by TCAs. Although SSRIs may have comparable efficacy and an improved safety profile compared with MAOIs, sufficiently powered studies are needed to recommend SSRIs as a first-line therapy for atypical depression. A hindrance to optimizing treatment outcomes in patients with atypical depression is that both first-line treatments are underprescribed due to adverse side effect profiles. However, the introduction of the selegiline patch may improve outcomes for patients with atypical depression. The results of studies with selegiline for atypical depression are eagerly awaited.

Drug names: fluoxetine (Prozac and others), imipramine (Tofranil and others), phenelzine (Nardil), selegiline (Eldepryl, Zelapar, and others), selegiline transdermal system (EMSAM), sertraline (Zoloft and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, selegiline is not approved by the U.S. Food and Drug Administration for the treatment of depression.

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