Venlafaxine in Treatment-Resistant Obsessive-Compulsive Disorder

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Background: While selective serotonin reuptake inhibitors (SSRIs) are the first-line treatment of obsessive-compulsive disorder (OCD), approximately 40% of patients fail to respond to SSRIs. Venlafaxine is a serotonin-norepinephrine reuptake inhibitor (SNRI) that might be effective in the treatment of OCD, even among those who have failed previous SSRI trials.

Method: Thirty-nine patients who met DSM-IV criteria for OCD, including 29 who were resistant to prior SRI treatment trials, were treated with venlafaxine in an open, naturalistic fashion. Improvement was assessed using the Clinical Global Impressions-Improvement scale.

Results: Of 39 patients treated with venlafaxine, 27 (69.2%) were rated as sustained treatment responders. Of the 29 patients who did not respond to 1 or more previous SRI trials, 22 (75.9%) were rated as having sustained response to treatment. Mean dose of venlafaxine was 232.2 mg/day (range, 37.5–375 mg/day), and it was generally well tolerated.

Conclusion: Venlafaxine may be beneficial to individuals with OCD, including those who have not responded to prior SSRI trials. However, these findings must be interpreted with caution, as the study is limited by its open, retrospective nature and its inclusion of patients with comorbid diagnoses and patients on concomitant medications. Prospective, controlled trials with a more homogeneous patient population are needed to replicate these preliminary findings.

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Obsessive-compulsive disorder (OCD) is often a chronic disorder associated with substantial impairment in functioning. The disorder is characterized by recurrent and intrusive thoughts, impulses, or images that cause marked distress, as well as repetitive behaviors performed in response to an obsession.[1] OCD is among the most common mental disorders, with a lifetime prevalence rate of 1.9% to 3% in the United States.[2] An even larger population may suffer from an obsessive-compulsive spectrum disorder (i.e., body dysmorphic disorder, trichotillomania, and Tourette's syndrome).[3]

Serotonin reuptake inhibitors (SRIs), which include selective serotonin reuptake inhibitors (SSRIs) and clomipramine, are considered to be the most effective pharmacologic treatments for OCD.[4] Clomipramine, fluoxetine, fluvoxamine, sertraline, and paroxetine have all been approved by the U.S. Food and Drug Administration (FDA) for the treatment of adult OCD.[5] Double-blind, placebo-controlled studies in OCD have demonstrated the efficacy of clomipramine,[6] fluoxetine,[7] fluvoxamine,[8–10] sertraline,[11,12] paroxetine,[13] and citalopram.[14]

Despite the successful treatment of many obsessive-compulsive individuals with SRIs, clinical trials have suggested that approximately 20%[15] to 40%[16] fail to respond to SRIs and exhibit significant impairment in functioning.[17–19] Among SRI-naive patients, response rates have been reported to range from 42%[20] to 53%.[21] SRI response rates in patients who failed a previous SRI trial are considerably lower (closer to 27%[20] or 33%).[21] Among OCD patients who had previously failed trials of clomipramine or fluoxetine, 19% responded to fluvoxamine.[22] Pallanti et al.[23] reported that 1(14%) of 7 patients who failed 2 SRI trials responded to the SRI citalopram. To date, there are no systematic data suggesting the best treatment strategy for these treatment-resistant OCD patients who have not responded satisfactorily to 1 or more SRI trials.

Clomipramine is a tricyclic antidepressant (TCA) that is a potent serotonin and norepinephrine reuptake inhibitor (SNRI) in addition to being an SRI.[4] Its efficacy has been demonstrated in a large, placebo-controlled study.[6] Data on clomipramine's superior efficacy to SSRIs in the treatment of OCD are mixed. Although several meta-analyses have shown that clomipramine is more effective

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than the SSRIs, head-to-head comparisons between clomipramine and individual SSRIs have shown no differences in efficacy.[4] Clomipramine is also associated with relatively high rates of side effects. Patients treated with clomipramine have been found to experience adverse events such as seizures (0.4% of patients) and elevated aminotransferase levels (6.9% of patients).[6] Other common side effects of clomipramine include postural hypotension, weight gain, and constipation.[24]

Venlafaxine, which also acts as an SNRI, has a more favorable side effect profile and lacks the undesirable anticholinergic, antihistamine, and α-adrenergic blocking effects of clomipramine.[24] Venlafaxine has been shown to be well tolerated in clinical trials at doses of up to 375 mg/day.[25] It should be noted that venlafaxine may cause elevations in supine diastolic blood pressure at higher doses, perhaps due to its noradrenergic pressor effects. A meta-analysis of major depression patients treated with venlafaxine showed that this elevation in supine diastolic blood pressure is only statistically significant in patients who are on venlafaxine doses of greater than 300 mg/day and that patients with preexisting high blood pressure were not adversely affected by venlafaxine treatment.[26] Nonetheless, patients who are taking venlafaxine doses of greater than 225 mg daily should be monitored for blood pressure elevations.

To date, few data are available with regard to the effect of venlafaxine in OCD. Several small-scale studies have suggested that venlafaxine may be effective in the treatment of OCD. In a 12-week open-label study of venlafaxine in the treatment of 10 patients with OCD, 3 patients were considered responders as measured by a 35% decrease in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score, while 4 patients were considered responders as measured by Clinical Global Impressions-Improvement (CGI-I) scores of 1 or 2.[27] An 8-week, double-blind, placebo-controlled study of venlafaxine in 30 outpatients with OCD suggested a trend of improvement according to CGI score among individuals who were treated with venlafaxine.[28] Venlafaxine treatment resulted in improvement in 6 of the 16 patients in the venlafaxine treatment group, while none of the patients in the placebo group showed an improvement. However, this study had a very high dropout rate and a very short treatment period.

Preliminary data suggest that venlafaxine may be as effective as clomipramine in the treatment of OCD. Response rates (defined as a 35% or greater decrease of Y-BOCS score or a CGI-I score of 1 or 2) in a recent study comparing the 2 medications among treatment-resistant OCD patients were as follows: 34.6% (9 patients of 26) for venlafaxine as compared to 42.5% (20 patients of 47) for clomipramine.[29] There was no statistically significant difference between the 2 groups. Patients treated with venlafaxine reported fewer side effects than patients in the clomipramine group.

In a study comparing 2 SNRIs, clomipramine and venlafaxine, and 1 SSRI, citalopram, in OCD patients who failed to respond to 2 previous SSRI trials, using a last-observation-carried-forward analysis (LOCF), 37.5% of patients responded to venlafaxine, and 27.3% responded to clomipramine, while only 11.1% responded to citalopram.[29] Using a visit-wise analysis, 42.8% of patients responded to venlafaxine, as compared to 37.5% who responded to clomipramine and 14.3% who responded to citalopram. These results suggest that venlafaxine may be effective not only in the treatment of OCD patients who have never taken an SSRI, but also in treatment-resistant OCD patients. The results of the above studies of venlafaxine in the treatment of OCD should be interpreted with caution as a result of their preliminary nature and their relatively small sample sizes.

METHOD

This open, retrospective, naturalistic study examined treatment response of venlafaxine in 39 patients with obsessive-compulsive disorder, of which 29 (74.4%) were resistant to prior SRI treatment trials. Efficacy was measured using the CGI-I.[30] The data are presented in a descriptive fashion.

Subjects

All patients with a primary diagnosis of OCD by DSM-IV criteria who were treated with both venlafaxine and venlafaxine extended-release (XR) were included. Patients were assessed by a board certified psychiatrist with expertise in the diagnosis and treatment of OCD and recruited from the authors' office-based practices. All patients were treated in New York in a private practice setting. The presence of comorbid psychiatric illness did not result in exclusion from the study if the comorbid diagnosis was considered to be a secondary diagnosis.

The 39 subjects included 22 males and 17 females, of which 5 were children/adolescents and 34 were adults. Their ages ranged from 12 to 78 years, with a mean age of 33.7 ± 15.0 years. Of the 39 patients in the study, 31 (79.5%) had comorbid diagnoses (Table 1). Thirty-six (92.3%) of 39 patients took concomitant medications, including atypical neuroleptics, benzodiazepines, and mood stabilizers, during the study. Prior to and throughout the study, all concomitant medications were maintained at stable doses.

Twenty-nine (74.4%) of the 39 patients were nonresponders to 1 or more previous SRI trials. Twenty-two (56.4%) of the 39 patients were nonresponders to 2 or more previous SRI trials.

Psychometric Instrument

Symptom improvement was assessed via the CGI-I, a clinician rated instrument that compares the patient's condition at the end of clinical treatment to that at baseline to

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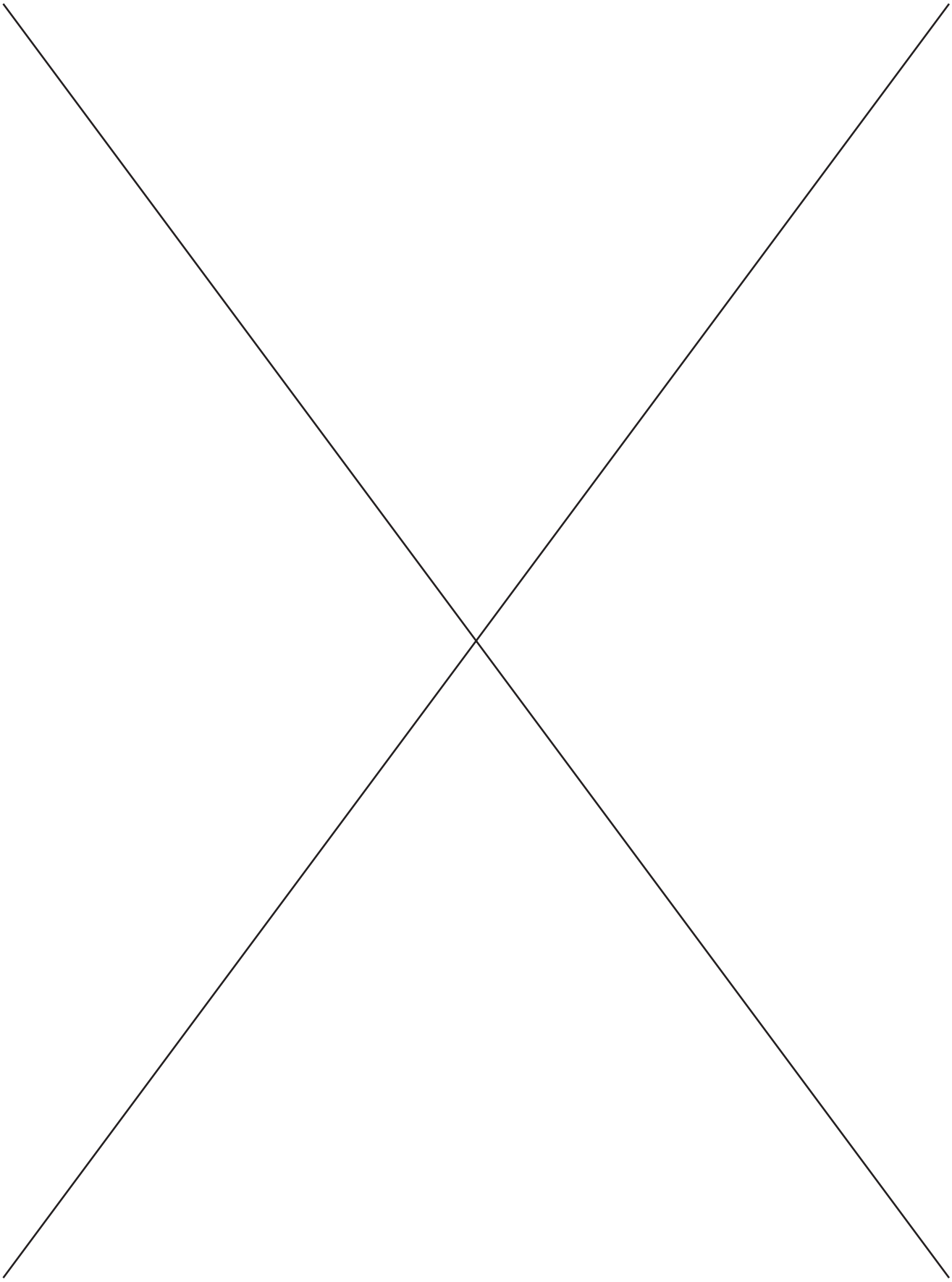

Table 1. Characteristics of 39 Patients With DSM-IV Obsessive-Compulsive Disorder[a]

Characteristic	N	%
Gender		
Female	17	43.6
Male	22	56.4
Secondary psychiatric diagnosis		
Mood disorder	18	46.2
Body dysmorphic disorder	11	28.2
Attention deficit disorder	10	25.6
Eating disorder	5	12.8
Social phobia	7	17.9
Tics	4	10.3
Panic disorder	3	7.7
Separation anxiety	2	5.1
Trichotillomania	2	5.1
Sexual addiction	2	5.1
Borderline personality disorder	2	5.1
Tourette's syndrome	1	2.6
Kleptomania	1	2.6
Generalized anxiety disorder	1	2.6
Concomitant medications		
Risperidone	15	38.5
Buspirone	9	23.1
Clonazepam	9	23.1
Gabapentin	9	23.1
Divalproex sodium	6	15.4
Dextroamphetamine	5	12.8
Lamotrigine	5	12.8
Trazodone	5	12.8
Methylphenidate	4	10.3
Lithium	3	7.7
Olanzapine	3	7.7
Topiramate	3	7.7
Alprazolam	2	5.1
Lorazepam	2	5.1
Bupropion	1	2.6
Haloperidol	1	2.6
Naltrexone	1	2.6
Phenelzine	1	2.6
Quetiapine	1	2.6
Sertraline	1	2.6
Thyroxine	1	2.6
Zaleplon	1	2.6
Prior SRI medication		
Fluoxetine	23	58.9
Fluvoxamine	15	38.5
Clomipramine	10	25.6
Sertraline	10	25.6
Paroxetine	8	20.5
Citalopram	1	2.6
Past SRI response		
Nonresponse to 1 or more SRIs	29	74.4
Nonresponse to 2 or more SRIs	22	56.4

[a]Age, mean ± SD = 33.7 ± 15.0 years.
Abbreviation: SRI = serotonin reuptake inhibitor.

determine global improvement. The scores range from 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse to 7 = very much worse. Responders were defined as those who obtained a CGI-I score of 1 to 2 (very much to much improved). The ratings were compiled by a study psychiatrist who used all available chart data to determine CGI-I scores. Because of the study's naturalistic nature, an OCD-specific scale such as the Y-BOCS was not utilized.

Table 2. Venlafaxine Treatment Responses in 39 Patients With Obsessive-Compulsive Disorder

Variable	Value
CGI-Improvement score, mean ± SD	1.9 ± 1.06
Length of treatment, mean ± SD, mo	18.1 ± 13.0
Highest dose, mean ± SD, mg/d	288.1 ± 103.7
Final dose, mean ± SD, mg/d	232.2 ± 97.0
Side effects, N (%)	
Fatigue/lethargy	16 (41.0)
Weight gain	7 (17.9)
Insomnia	6 (15.4)
Digestive disturbances	6 (15.4)
Sexual side effects	5 (12.8)
Sweating	4 (10.3)
Tremor	4 (10.3)

Abbreviation: CGI = Clinical Global Impressions.

Medication Administration

Patients were started on venlafaxine, usually at 37.5 to 75 mg/day. Doses were subsequently flexibly titrated up and adjusted to minimize side effects and maximize improvement. At each visit, patients were asked about potential side effects. Patients were urged to follow their blood pressure on medication doses greater than 225 mg/day. Data from all 39 patients are included in the report.

RESULTS

Subjects were treated with venlafaxine for a mean of 18.1 ± 13.0 months (range, 1–56 months) and reached a mean highest dose of 288.1 ± 103.7 mg/day (range, 37.5–450 mg/day). The mean final dose was 232.2 ± 97.0 mg/day (range, 37.5–375 mg/day). Thirty-two (82.1%) of the patients reached a highest dose of 225 mg or greater, and 28 (71.8%) of the patients reached a final dose of 225 mg or higher (Table 2).

Twenty-seven (69.2%) of 39 patients were rated as sustained treatment responders, with final CGI-I scores of much improved (score of 2) or very much improved (score of 1) (Table 3). The mean CGI-I score for the entire group of patients was 1.9 ± 1.06 (much improved). Twelve (30.8%) of 39 patients were rated as treatment nonresponders, with CGI scores ranging from 3 to 4 (Table 3). Mean highest venlafaxine dose for treatment responders (296.3 ± 94.0 mg/day) did not significantly differ compared to nonresponders (269.8 ± 125.4 mg/day). The mean final dose also did not differ for responders (237.7 ± 85.8 mg/day) compared to nonresponders (219.8 ± 121.7 mg/day). Side effects of venlafaxine in this sample were mostly mild to moderate, and included fatigue/lethargy (N = 16), weight gain (N = 7), insomnia (N = 6), digestive disturbances (N = 6), and sexual side effects (N = 5). However, since most patients in this sample were taking concomitant medications during the study, it is difficult to determine whether these side effects are a result of venlafaxine, the concomitant medication, or an interaction between venlafaxine and a concomitant

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Table 3. Venlafaxine Response in Obsessive-Compulsive Disorder Patients

	All Patients (N = 39)		Prior SRI Nonresponders (N = 29)	
CGI-Improvement Score	Frequency	Percentage	Frequency	Percentage
Responders	27	69.2	22	56.4
1 (very much improved)	19	48.7	16	41.0
2 (much improved)	8	20.5	6	15.4
Nonresponders	12	30.8	7	17.9
3 (minimally improved)	8	20.5	5	12.8
4 (no change)	4	10.3	2	5.1

Abbreviations: CGI = Clinical Global Impressions, SRI = serotonin reuptake inhibitor.

medication. Three patients (7.7%) were discontinued from medication as a result of side effects.

Of the 29 patients who did not respond to 1 or more previous SRI trials, 7 (24.1%) were rated as treatment nonresponders, and 22 (75.9%) were rated as sustained treatment responders (Table 3). Of the 22 patients who had previously not responded to 2 or more SRI trials, 4 (18.2%) were rated as treatment nonresponders, and 18 (81.8%) were rated as sustained treatment responders.

Thirty-one (79.5%) of the 39 patients had secondary comorbid diagnoses. Twenty-two (71.0%) of the 31 patients with comorbid diagnoses were rated as sustained treatment responders. Of the 39 patients, 36 were on concomitant medications during the study. Twenty-five (69.4%) of the 36 patients on concomitant medications were rated as sustained treatment responders.

DISCUSSION

This open, retrospective pilot study provides preliminary evidence that venlafaxine may be beneficial to individuals with OCD, including those who have not responded to prior SRI trials. In addition, venlafaxine was well tolerated by most of the participants in this study.

The findings from this study must be interpreted with caution. The study is limited by its open, retrospective nature and its inclusion of patients with secondary comorbid psychiatric diagnoses and patients who were on concomitant medications. The open nature of this study may partially account for the higher rate of response than reported in earlier double-blind SRI trials in OCD. However, there is a paucity of studies of real-life patients who have failed previous SRI trials. Most clinical trials exclude patients with comorbid diagnoses as well as patients who are taking concomitant medications. Advantages of the naturalistic nature of the current study include patients who represent the patient population that clinicians typically encounter who are well studied and treated for a long period of time.

These data suggest that venlafaxine may be effective in treating OCD patients, even those with comorbid diagnoses and those who are nonresponders to other SRI medications. Twenty-seven (69.2%) of 39 OCD patients who were treated with venlafaxine showed global improvement. Patients with comorbid diagnoses, secondary OCD, and prior SRI nonresponse had similar rates of response to venlafaxine. Interestingly, 3 of the 4 patients with secondary comorbid tics were rated as nonresponders to venlafaxine.

At the doses used in this study (maximum = 288.1 mg/day; final dose = 232.2 mg/day), venlafaxine does have a clinically relevant noradrenergic effect.[31] However, direct in vivo comparisons to the noradrenergic potency of clomipramine are problematic due to factors such as differences in protein-binding and lack of direct comparisons between clomipramine and venlafaxine. In comparison to SSRIs whose cerebrospinal fluid (CSF) concentrations range from 7–35 nM, the CSF concentration of venlafaxine ranges from 100–850 nM.[32] The inhibitory constant (K_i) values for 5-HT blockade for SSRIs range from 0.7–14 nM, while for venlafaxine, K_i is approximately 39 nM. For norepinephrine blockade, K_i values for SSRIs range from 33–3000 nM, while for venlafaxine, it is approximately 210 nM.[32]

Given our findings that, overall, 69.2% of the patients who were treated with venlafaxine exhibited global improvement, a prospective, double-blind, placebo-controlled trial, in a more homogeneous patient population, is needed to replicate these promising but preliminary findings.

Drug names: alprazolam (Xanax and others), bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa), clomipramine (Anafranil and others), clonazepam (Klonopin and others), dextroamphetamine (Dexedrine and others), divalproex sodium (Depakote), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigine (Lamictal), lorazepam (Ativan and others), methylphenidate (Ritalin, Concerta, and others), naltrexone (Depade), olanzapine (Zyprexa), paroxetine (Paxil), phenelzine (Nardil), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), thyroxine (Synthroid, Novothyrox, and others), topiramate (Topamax), trazodone (Desyrel and others), venlafaxine (Effexor), zaleplon (Sonata).

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