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**Clinical Characteristics and Management of Treatment-Resistant Depression**

**To the Editor:** Approximately one-third of patients with major depressive disorder (MDD) are treatment resistant.<sup>1,2</sup> Despite high prevalence, the clinical characteristics and management of treatment-resistant depression (TRD) are not well described. We present a comprehensive clinical description of a case series of 79 well-characterized patients with TRD referred to a university-based TRD specialty clinic.

**Method.** Of 104 patients referred to our TRD clinic from 2009 to 2014, 79 met clinic inclusion criteria: *DSM-IV-TR*-defined MDD with resistance to  $\geq 3$  antidepressant trials of adequate dose and duration and no diagnoses of bipolar I or II disorder, personality disorder, psychotic disorder, or alcohol or drug abuse/dependence. Medical records for psychiatric treatments within at least 5 years were obtained. Psychiatric history, including symptom, clinical, family, and treatment information, was obtained at the initial visit. Patients completed the Montgomery-Asberg Depression Rating Scale (MADRS).<sup>3</sup> Institutional review board approval and patient consent were obtained for research use of data.

**Results.** Of the 79 patients, 67% (n=53) were women; the mean age was 49.3 years (SD=14.2). One-third (n=26) were receiving disability support. The mean age at MDD onset was 24.3 years (SD=13.8), with 50% of patients reporting MDD onset after age 18. The mean number of lifetime MDD episodes was 2.6 (SD=1.7), with 70% (n=55) of patients reporting  $\geq 2$  episodes; 30% (n=24) reported 1 sustained MDD episode. The mean number of lifetime MDD years was 18.6 (SD=10.0), with 51% (n=40) of patients reporting  $\geq 18$  years. Most patients, 63% (n=50), reported at least 1 psychiatric hospitalization; 21% (n=17) reported  $\geq 4$  hospitalizations (maximum=20). Of those hospitalized at least once, the mean number of hospitalizations was 3.8 (SD=4.3); 43% (n=34) of all patients reported  $\geq 2$  hospitalizations. At least 1

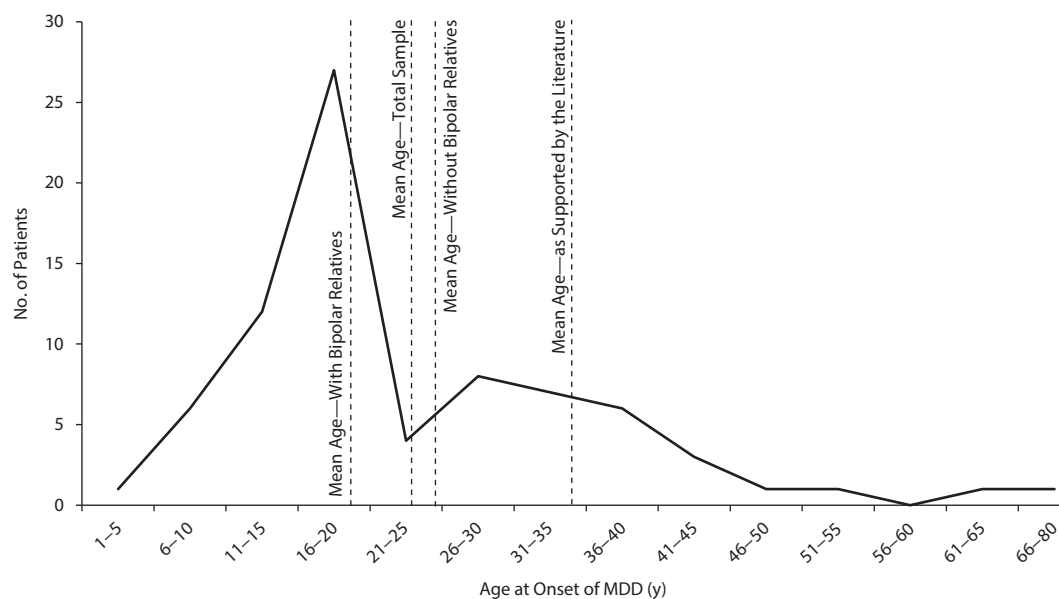
suicide attempt was reported by 27% (n=21); the mean number of attempts was 3.4 (SD=4.3), and 50% had  $\geq 2$ .

Regarding family history, 62% (n=49) and 42% (n=33) reported a first- or second-degree relative with MDD, respectively; these values were 14% (n=11) and 8% (n=6), respectively, for bipolar disorder. Younger age at MDD onset was associated with more first- and second-degree relatives with mood disorder ( $r=-0.26$ ,  $P=.024$ ). A strong early-onset association was also seen when comparing TRD patients with first- and second-degree relatives with bipolar disorder (mean=18.3 years, SD=6.7, n=16) versus those without (mean=25.7 years, SD=14.7, n=62;  $t=2.9$ ,  $P=.005$ ) (Figure 1). Mean MADRS score (range, 0–60) was 29.6 (SD=8.5), with 62% (n=49) and 28% (n=22) in the moderate (20–34) and severe ( $\geq 35$ ) range, respectively.

The mean number of antidepressant medication trials was 8.0 (SD=3.3). Antidepressant classes included selective serotonin reuptake inhibitor (SSRI), 99% (n=78), with 3.6 mean trials (SD=1.5); serotonin-norepinephrine reuptake inhibitor, 95% (n=75); bupropion, 89% (n=70); tricyclic, 57% (n=45); mirtazapine, 53% (n=42); and monoamine oxidase inhibitor (MAOI), 37% (n=29). Other treatments included electroconvulsive therapy (ECT) (60%, n=47), omega-3 fatty acids (32%, n=25), herbal medicines (21%, n=17), phototherapy (20%, n=16), vagus nerve stimulation (10%, n=8), and transcranial magnetic stimulation (6%, n=5). Antipsychotic medication augmentation was used by 86% (n=68): aripiprazole, 66% (n=52); quetiapine, 58% (n=46); olanzapine, 35% (n=28); and ziprasidone, 25% (n=20). Other augmentation agents included lithium, 58% (n=46); stimulants, 54% (n=43); thyroid, 34% (n=27); and buspirone, 23% (n=18). The mean number of lifetime psychotropic medications was 16.4 (SD=8.1). Most patients had engaged in (94%, n=74) or continued to be engaged in (56%, n=44) psychotherapy.

Several important observations emerged from this large case series of carefully screened/selected TRD patients. Similar to other

**Figure 1. Age at Onset of Depression**



Abbreviation: MDD= major depressive disorder.

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investigations, this series demonstrated that the average age at TRD onset was appreciably earlier, 24.3 years, compared to the conventionally reported mean MDD age at onset (averaging 30 and 40 years of age for women and men, respectively).<sup>4-6</sup> As previously reported, we found that early MDD onset was associated with a stronger family history of mood disorders, particularly bipolar disorder.<sup>7</sup> The high prevalence of bipolar family history suggests that a significant subset of TRD patients (20% in this series) may have an unrecognized bipolar disorder variant.<sup>8</sup> However, most patients (58%) in the sample had failed lithium augmentation trials. TRD was highly familial: 62% of TRD patients reported first-degree relatives with unipolar MDD (in contrast, previously reported MDD risk in first-degree relatives of unipolar depressed probands was 5.1%–17.5%).<sup>9</sup> TRD carries high suicide attempt risk: 27% of patients reported at least 1 suicide attempt, consistent with other reports of 31%, which was greater than the attempted suicide rate of 15% in non-TRD MDD patients.<sup>10</sup>

The TRD patients were notable for multiple failed SSRI trials, suggesting that repetitive (>3) SSRI trials in MDD may not be warranted.<sup>11</sup> More aggressive antidepressant treatments with potential efficacy in TRD were seemingly underutilized, including ECT (60%) and MAOIs (37%). The reason for the underuse of these more aggressive treatments was not clear. Recent reports suggest that fewer facilities offer ECT.<sup>12</sup> Anecdotally, many of our TRD patients reported never having been offered ECT (no recorded incidence). Recent reviews suggest lack of MAOI marketing, clinician fears (of medical complications), and no experience in MAOI use as possible reasons for MAOI underuse.<sup>13-16</sup> Clinical use of MAOIs requires an antidepressant washout period of 2 weeks (6 weeks for fluoxetine) and adherence to a low-tyramine diet.<sup>13</sup>

Study limitations include no structured clinical interviewing (standard clinical interviews were performed), comparison of results to estimates from the literature and not to a non-TRD comparison group, and limited generalizability because all but 1 patient was insured and no patients had personality disorder or substance abuse diagnoses.

In conclusion, successful identification and management of TRD may require that psychiatrists receive training about use of aggressive antidepressant treatments, avoidance of redundant antidepressant medications, and appreciation for familial contributions. Such management could be achieved through specialty TRD clinics, similar to models of care for diabetes and epilepsy, to characterize each TRD patient's course of illness/treatment history.

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