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## Clinicians' Views on Treatment-Resistant Depression: 2016 Survey Reports

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### Abstract

**Background**—There is a relative paucity of information on both empirical and subjective treatment strategies for treatment-resistant depression (TRD), especially in late life. This paper reviews the findings from two 2016 surveys conducted through the American Psychiatric Association publication the *Psychiatric Times* and via a member survey by the American Association for Geriatric Psychiatry (AAGP).

**Methods**—We present the results of the two surveys in terms of descriptive frequencies and percentages and discuss the strengths and weaknesses of various approaches to late-life TRD.

**Results**—The *Psychiatric Times* survey received 468 responses, and the AAGP survey received 117 responses, giving an overall sample of 585 responses. The majority (76.3%) of respondents from both groups believed that a large randomized study comparing the risks and benefits of augmentation and switching strategies for TRD in patients aged 60 years and older would be helpful, and 80% of clinicians believed their practice would benefit from the findings of such a study. Of the treatment strategies that need evidence of efficacy, the most popular options were augmentation/combination strategies, particularly augmentation with aripiprazole (58.7%), bupropion (55.0%), and lithium (50.9%).

**Conclusions**—Late-life TRD constitutes a large proportion of clinical practices, particularly of geriatric psychiatry, with lacking evidence of efficacy of most treatment strategies. These surveys

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indicate a clear need for a large randomized study that compares risks and benefits of augmentation and switching strategies.

### Keywords

depression; late-life; treatment; survey

Depression is a major public health issue, and is associated with significant mortality, morbidity, and economic burden. It is the third-greatest contributor to global disease burden<sup>1</sup> and affects both low- and high-income countries with a 12-month prevalence of 5.9% and 5.5%, respectively.<sup>2</sup> Depression is projected to hold the greatest illness burden in high-income countries by 2030,<sup>1</sup> and it is therefore paramount to develop a coordinated strategy for its treatment. The economic cost of depression in the United States is estimated to be \$210.5 billion, with 45% attributable to direct medical costs, 5% to suicide-related costs, and 50% to indirect workplace costs (i.e., loss of productivity through absenteeism and presenteeism<sup>3</sup>).

Treatment-resistant depression (TRD) is defined as failure to achieve disease remission with adequate trials of two or more pharmacologically dissimilar antidepressants, and accounts for 12%–20% of depression cases.<sup>4,5</sup> It is believed to arise from biological incompatibility between the molecular basis of an individual's depression and the antidepressant used to treat it, and/ or due to a comorbidity hindering antidepressant effect, such as psychiatric comorbidity, childhood trauma, or personality disorder.<sup>6</sup> Fewer than 55% of patients achieve remission with first and second trial of antidepressants, meaning a significant portion of depression does not respond to conventional treatment guidelines.<sup>7</sup>

There is a relative paucity of information on treatment options and efficacy in TRD, especially in late life. This paper reviews the findings of a clinician survey on TRD, conducted by the *Psychiatric Times* and the American Association of Geriatric Psychiatry (AAGP), and discusses both strengths and weaknesses of various approaches to TRD.

### Methods

A brief online survey on clinician attitudes towards TRD was composed by the OPTIMUM co-investigators and edited by the editors of the *Psychiatric Times* and the AAGP research committee. Both surveys used identical questions. The surveys were both conducted in January 2016. The *Psychiatric Times* distributed the survey through an e-blast to 100,000 Web subscribers. A notification of the survey was also in the printed journal, which has a subscribership of 40,000. The AAGP distributed the survey through an e-mail to 1,355 subscribers. The survey sought information about practice location, work setting, years in practice; proportion of treatment-resistant patients in practice, including those 60 years and older; and the need to acquire evidence of efficacy for a variety of augmentation or switching strategies was obtained from both groups of clinicians. Half of the questions had set answers to choose from, and half were free-text. Data were pooled from both surveys unless otherwise stated.

## Results

The *Psychiatric Times* survey received 468 responses (0.47% response rate), and the AAGP survey received 117 responses (8.63% response rate); the overall sample size was 585. Those participating in the surveys represented a variety of clinical backgrounds and work settings, as detailed in Table 1.

The United States was well represented in the surveys, contributing 80.1% of responses from across the Northeast (26.1%), Southeast (16.7%), Midwest (18.1%), Southwest (7.5%) and West (12.5%) regions of the country. The remaining 19.1% of responses came from 41 countries, including Australia, the UK, Canada, and India. Both sides of the experience spectrum were represented, with 33.8% of respondents in their first decade of practice, and 35.8% having practiced for more than 25 years. The balance of genders was marginally in favor of female respondents. The respondent demographics are broken down further in Table 2.

Two-thirds of respondents reported that TRD accounted for up to one-quarter of their practice, and an additional 20.8% reported that it accounted for up to one-half of their practice (Table 3). Patients aged 60 years or over accounted for 10%–25% of the TRD workload in 32% of practices, and this was the mode response. General psychiatrists responding to the *Psychiatric Times* survey responses indicated a lower proportion of older TRD patients in their practices compared with the AAGP survey responses, indicating that geriatric psychiatrists carry the heaviest load of treating these patients. The aggregate results are illustrated in Figures 1 and 2.

The majority (76.3%) of respondents in both groups believe that a large randomized study comparing the risks and benefits of augmentation and switching strategies for TRD in patients aged 60 years and older would be helpful, of which more than one-third would find it extremely helpful, as outlined in Table 4. Importantly, four in five clinicians believe that their practice would benefit from the findings of such a study.

When offered a choice of treatments to be studied, the most popular options were augmentation strategies—namely, augmentation with aripiprazole (58.7%), bupropion (55.0%), and lithium (50.9%). Switching to bupropion and nortriptyline were less popular, as seen in Table 4.

The *Psychiatric Times* offered respondents an opportunity to suggest an alternative treatment to be studied, and just less than one-third of survey takers took this opportunity. The most common suggestions were psychotherapy, augmentation with antipsychotics, transcranial magnetic stimulation and deep brain stimulation, electroconvulsive therapy, addition of a second antidepressant both typical (selective serotonin reuptake inhibitors [SSRIs], serotonin noradrenalin reuptake inhibitors [SNRIs], tricyclic antidepressants, and monoamine oxidase inhibitors) and atypical (mirtazapine) as well as newer agents (vortioxetine), use of methylphenidate and other stimulants, ketamine, and lamotrigine. Several respondents suggested supplementation of thyroid hormone, and less frequently, folate and omega 3. Other drugs named were memantine, pramipexole, pindolol, nefazodone, buspirone, and

glutamnergic treatment. Finally, lifestyle measures such as exercise and various complementary and alternative practices, including acupuncture, were also suggested.

## Discussion

The findings of this survey support reported rates of TRD of 10%–25% in community samples. In older adults, depression is more likely to follow a chronic or relapsing course,<sup>8</sup> and 55%–81% of older adults with major depressive disorder fail to respond to an SSRI or SNRI.<sup>9</sup> Depression in older age is an important risk factor for all-cause dementia,<sup>10</sup> and is associated with higher utilization of health care services, caregiver burden, and suicide rates.<sup>11,12</sup>

The findings of our survey support TRD being a significant unresolved issue in practices of general and geriatric psychiatrists. Previous studies, including STAR\*D, VAST-D, PRedICT and iSPOT-D, have explored treatment of TRD in young adults, yet there is a relative paucity of research in the management of TRD in older adults (also known as TRDOA).<sup>13</sup> Global aging of the population brings this undertreated population to the forefront of the attention of both clinicians and researchers. This view is shared by 76.3% of our survey respondents.

In general TRD populations, a meta-analysis reviewing 48 trials of augmentation agents found that quetiapine, aripiprazole, thyroid hormone, and lithium were significantly more effective than placebo in treatment, notwithstanding tolerability issues with antipsychotics and lithium, and safety issues with thyroid hormone supplementation.<sup>14</sup> In TRDOA, a double-blind randomized control trial of aripiprazole to augment venlafaxine therapy achieved 12 weeks of sustained remission in almost half the participants assigned to the intervention group, with a number needed to treat of 6.6.<sup>9</sup> The use of aripiprazole in older adults was associated with mild and transient akathisia and Parkinsonism, typically tremor, but not associated with cardiometabolic side effects, QTc prolongation, or increased suicidal ideation.<sup>9</sup> In this same study, severe baseline anxiety and cognitive inflexibility were associated with reduced remission rates.<sup>15</sup> These findings demonstrate that aripiprazole has good outcomes, tolerability, and safety in TRDOA.

## Conclusions

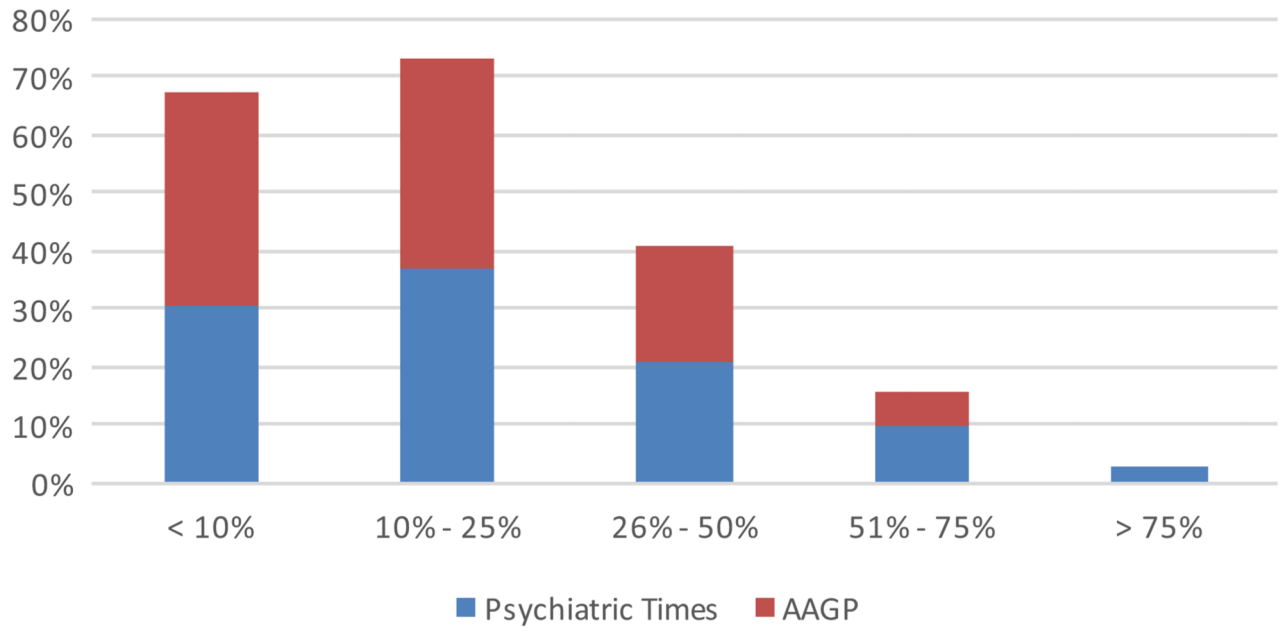
TRD is clearly a major burden to communities and health services. In the general adult population, there are a number of promising treatment strategies for TRD in development including ketamine, novel compounds, somatic treatments and brain stimulation treatment options, complementary and integrative treatment modalities, and pharmacogenetics guidance. There is a clear need for more randomized studies that explore novel treatments, and compare risks and benefits of different combination strategies.

## Acknowledgments

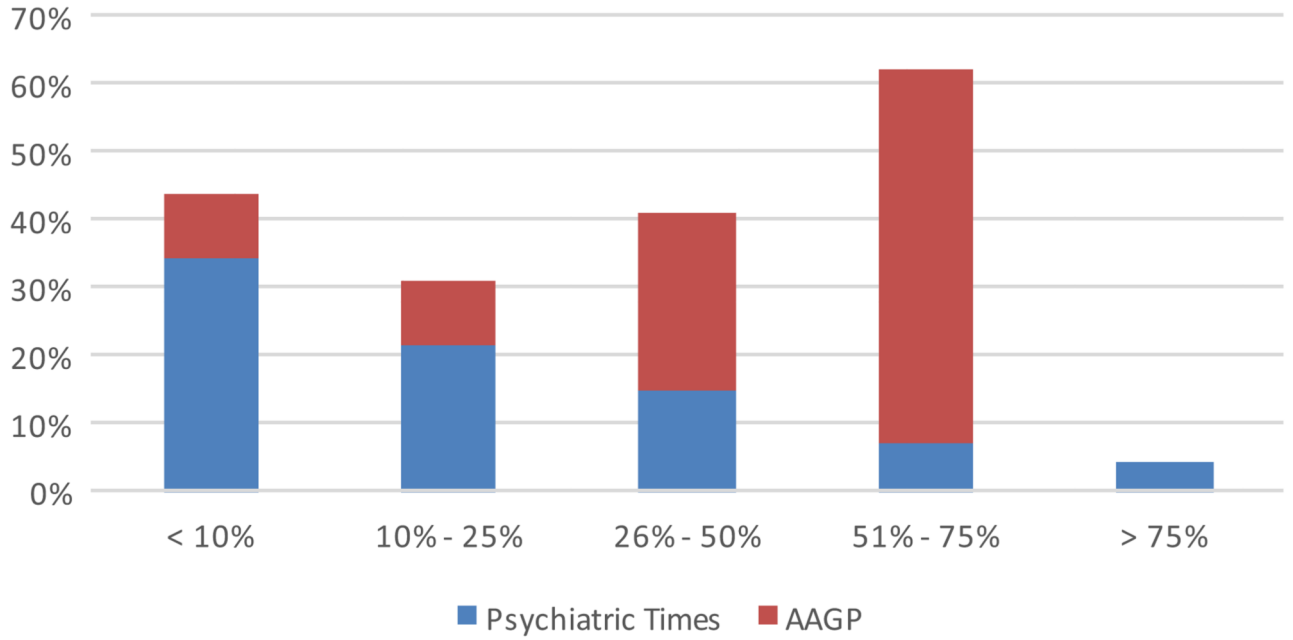
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**Figure 1. TRD workload as a percentage of total practice**



**Figure 2. TRDOA workload as a percentage of TRD practice**

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**Table 1**  
**Respondent Field of Practice or Work Setting**

<i>Psychiatric Times</i>	
<b>Primary Field of Practice</b>	<b>% Responses (N = 465)</b>
General psychiatry	45.8
Child psychiatry	1.9
Geriatric psychiatry	3.9
Psychology	7.7
Other mental health professional	14.0
Student / Resident	4.3
Other (please specify)	22.4
<b>AAGP</b>	
<b>Work Setting</b>	<b>% Responses (N = 110)</b>
Individual clinical practice	25.5
Healthcare system	49.1
Academic	57.3
Teaching	32.7
Individual clinical practice	25.5

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**Table 2**  
**Respondent Demographics**

	<i>Psychiatric Times</i> , N	AAGP, N	Aggregate (N, %)
Years in practice			
0–5	102	26	128 (22.2%)
6–10	53	14	67 (11.6%)
11–15	48	10	58 (10.1%)
16–20	49	15	64 (11.1%)
21–25	40	13	53 (9.2%)
25 +	167	39	206 (35.8%)
	N = 459	N = 117	Total N = 576
Sex			
Male	206	62	268 (47.4%)
Female	243	54	297 (52.6%)
	N = 449	N = 116	Total N = 565
Location			
Northeast	115	35	150 (26.1%)
Southeast	74	22	96 (16.7%)
Midwest	79	25	104 (18.1%)
Southwest	37	6	43 (7.5%)
West	58	14	72 (12.5%)
Outside of United States	95	15	110 (19.1%)
	N = 458	N = 117	Total N = 575

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**Table 3**  
**TRD Prevalence and Patient Age Demographics**

	<i>Psychiatric Times</i> , N	AAGP, N	Aggregate (N, %)
% patients with TRD			
<10%	136	43	179 (31.6%)
10%–25%	166	42	208 (36.7%)
26%–50%	95	23	118 (20.8%)
51%–75%	43	7	50 (8.8%)
>75%	11	<i>a</i>	11 (1.9%)
	N = 451	N = 115	Total N = 566
% TRD patients aged			
60 + years			
<10%	187	9	196 (26.5%)
10%–25%	118	9	127 (32.0%)
26%–50%	82	25	107 (21.9%)
51%–75%	39	53	92 (17.6%)
>75%	25	<i>a</i>	25 (2.0%)
	N = 547	N = 96	Total N = 547

Note:

<sup>a</sup>Not an answer option in this survey.

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**Table 4**  
**Respondent Views on Large Randomized Study Comparing Augmentation and Switching Strategies for TRD patients Aged 60 + Years**

	<i>Psychiatric Times</i>	<b>AAGP</b>	<b>Aggregate (N, %)</b>
Perceived helpfulness rating			
1 (Not helpful)	17	93	110 (19.2%)
2	26	<i>a</i>	26 (4.5%)
3 (Helpful)	86	22	108 (18.8%)
4	127	<i>a</i>	127 (22.2%)
5 (Very helpful)	201	1	202 (35.3%)
	N = 457	N = 116	Total N = 573
Preferred treatments to be studied			
Augmentation with aripiprazole	240	91	331 (58.7%)
Augmentation with bupropion	222	88	310 (55.0%)
Augmentation with lithium	204	83	287 (50.9%)
Switching to bupropion	128	46	174 (30.9%)
Switching to nortriptyline	128	56	184 (32.6%)
Other (please specify)	159	<i>a</i>	159 (28.2%)
	N = 451	N = 113	Total N = 564
Perceived to benefit clinician's practice			
Yes	347	106	453 (79.9%)
No	28	0	28 (4.9%)
Not sure	78	8	86 (15.2%)
	N = 453	N = 114	Total N = 567

Note:

<sup>a</sup>Not an answer option in this survey.