

# Antidepressant Use in Patients with Major Depressive Disorder: A Comparison of Treatment Resistant and Non-Treatment Resistant Episodes in the United Kingdom Using the CPRD Database

Nicole Kubitz<sup>1</sup>, Ravi Potluri<sup>2</sup>, Maneesha Mehra<sup>3</sup>

<sup>1</sup>Janssen-Cilag GmbH, Neuss, Germany, <sup>2</sup>SmartAnalyst Inc., New York, NY, USA, <sup>3</sup>Janssen Global Services, Raritan, NJ, USA

## INTRODUCTION

- Major Depressive Disorder (MDD) is a globally prevalent chronic mood disorder with a significant disease burden. The Global Burden of Disease 2013 study estimated the global prevalence to be 25.3 million cases in 2013. It was ranked second in the list of the 25 leading causes of years lived with disability (YLD) with a mean of 51.8 million YLDs, which represented a 53% increase from 1990, when it was ranked third.<sup>1</sup> In the United Kingdom, it was the fourth leading cause of YLD in 2013.<sup>1</sup>
- The economic burden of MDD is also significant – the total annual cost of depression in Europe in 2004 was estimated to be 118 billion Euros, with direct and indirect costs totaling 42 billion and 76 billion Euros, respectively.<sup>2</sup>
- A subset of patients with MDD is characterized as having Treatment Resistant Depression (TRD), with the European Union's Committee for Human Proprietary Medicinal Products (CHMP) stating that 'a patient is considered therapy-resistant (TRD) when consecutive treatments with two different antidepressant products, used for a sufficient length of time at an adequate dose with adequate affirmation of treatment adherence, fail to induce a clinically meaningful improvement'.<sup>3</sup>
- The clinical and economic burden of TRD is significantly higher than of MDD.
  - Prevalence of comorbidities including anxiety disorders, chronic pain, and fibromyalgia was significantly higher in patients with likely TRD (20.5%, 23.2%, and 6.4%, respectively) than in non-TRD patients (12.6%, 14.5%, and 3.0%, respectively).<sup>4</sup>
  - Costs of medical services associated with TRD have been reported to be more than twice those associated with MDD (\$10,954 vs \$5,025).<sup>5</sup>
  - Patients with TRD have been found to be twice as likely as those with MDD to be hospitalized, with health care costs for hospitalized TRD patients being 6-fold higher than for non-TRD patients.<sup>6</sup>
- We analyzed the use of antidepressants (AD) during TRD and non-TRD episodes among MDD patients in the UK Clinical Practice Research Datalink (CPRD) between 2000 and 2012.

## RESULTS

- Of the 427,467 unique MDD patients for whom data were available, 136,079 (31.8%) were retained, while 291,388 (68.2%) were excluded because they lacked an index diagnosis, met an exclusion diagnosis criterion, did not meet age criteria, or had missing age or gender information (Table 1).

Table 1. Patient Inclusion and Exclusion Data

	Number of Patients	Proportion	
<b>Number of unique patients for whom data was available</b>	427,467	100%	
Number of patients excluded	Had an exclusion diagnosis during the evaluation period	4,984	1.2%
	Index date could not be found	264,243	61.8%
	Age < 18 years	2,202	0.5%
	Age > 65 years	19,951	4.7%
	Missing age or gender information	8	0.0%
<b>Number of patients retained in the analysis</b>	<b>136,079</b>	<b>31.8%</b>	

- One in 20 (6,311 [5.15%]) distinct MDD episodes with one or more ADAP prescription were treatment-resistant, with 6,221 (5.9%) of all MDD patients experiencing at least one TRD episode (Table 2).

Table 2. Proportion of TRD Patients and Episodes by Age and Gender

	% TRD Patients						Overall
	Male			Female			
Age (in years) →	18-35	36-50	51-64	18-35	36-50	51-64	
Number of MDD patients	17,747	17,684	10,455	40,365	32,618	17,210	136,079
Number of TRD patients that have at least 1 ADAP prescription	12,979	13,827	8,347	30,052	26,448	10,072	105,725
Proportion of patients that have at least 1 TRD episode out of those that have at least 1 ADAP prescription*	5.8% (747)	6.4% (887)	6.3% (522)	5.4% (1,619)	6.2% (1,629)	5.8% (817)	5.9% (6,221)

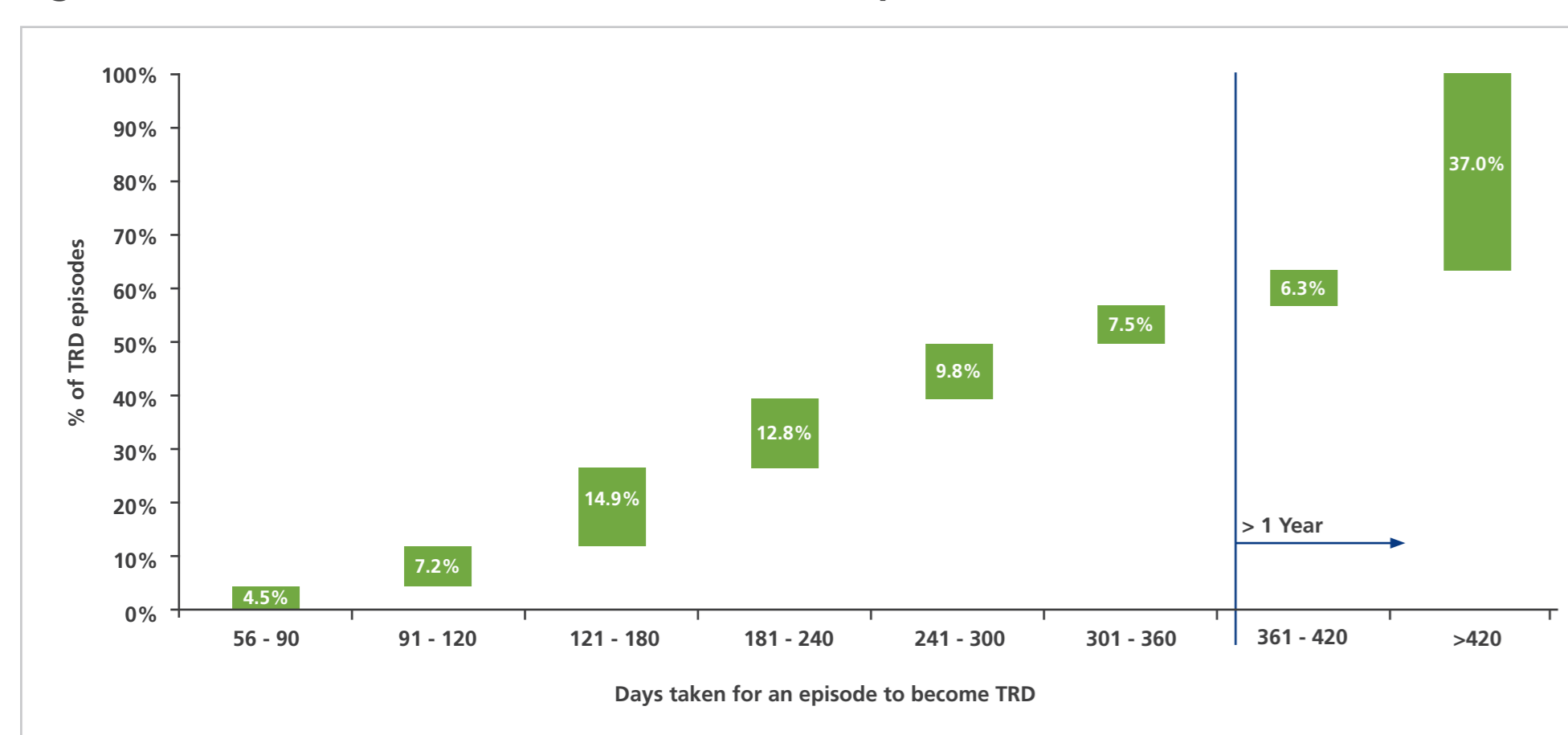
  

	% TRD Episodes						Overall
	Male			Female			
Age (in years) →	18-35	36-50	51-64	18-35	36-50	51-64	
Number of MDD episodes	21,048	20,802	12,104	49,666	39,841	20,199	163,660
Number of episodes that have at least 1 ADAP prescription	15,053	15,961	9,450	36,118	31,730	16,316	124,628
Proportion of TRD episodes out of all episodes that have at least 1 ADAP prescription*	5.0% (759)	5.7% (902)	5.6% (525)	4.6% (1,646)	5.2% (1,655)	5.1% (824)	5.1% (6,311)

\*Figures in parentheses represent number of patients  
\*Figures in parentheses represent number of episodes  
ADAP, anti-depressant and anti-psychotic/anti-manic drugs; MDD, major depressive disorder; TRD, treatment-resistant depression

- More than 50% of TRD episodes became so within one year after the start of the episode (Figure 1). The median time to development of TRD was <11 months (307 days; range 174-412 days), while the mean time to development of TRD was 503 days.

Figure 1. Distribution of Time Taken for a TRD Episode to Become So



TRD, treatment-resistant depression

## REFERENCES

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## METHODS

### STUDY POPULATION

- Adults, aged between 18 and 65 years, with an MDD diagnosis were considered for the analysis. Patients were excluded if:
  - They had an exclusion diagnosis during the evaluation period (detailed list of exclusion and inclusion diagnoses ICD-9 codes is available from the authors upon request).
  - An index diagnosis date could not be found – ie, if one of the two following conditions was not met for any MDD diagnosis claim:
    - 120-day clear history with no AD prescription and other inclusion diagnosis.
    - Continuous eligibility for the 28-month period starting 4 months prior to the diagnosis date.
- Information on age or gender was missing.

### STUDY DESIGN

- Business rules centered on diagnoses and on use of antidepressants were used to identify new MDD episodes and to define TRD.
- An MDD episode was defined as an episode commencing on an index diagnosis date and ending 120 days after the last diagnosis date or AD prescription claim.
  - An index diagnosis date was one that was not preceded by any inclusion diagnosis or an AD prescription claim in the preceding 120 days.
  - A patient may have had multiple index diagnosis dates, and thus may have had multiple new episodes.

- The definition of treatment-resistant depression was governed by the following rules:
  - All distinct regimens in an episode were deemed failures, except:
    - the very last regimen of the episode.
    - if any regimen had an immediately succeeding step-down regimen (ie, one or more of the products were discontinued while no other product was added), assuming this was applicable to all the instances in which the regimen appeared.
  - If there were two or more distinct failed regimens in an episode, the entire episode was categorized as a TRD episode.
  - In this context, a regimen was defined as the combination of anti-depressant and anti-psychotic/anti-manic (ADAP) drugs that were concurrently valid at a given time. The list of ADAP drugs used for this purpose is available from the authors upon request.
- A regimen/line of treatment (LOT) was governed by the following rule:
  - Non-ADAP drugs were not considered when determining regimens/LOTs, not only for the purpose of categorizing episodes as TRD but also for duration or switch analysis.
- Additional business rules relating to grace periods for drugs and regimens were applied in defining a TRD patient.
- The difference of proportions test was used, at a significance level of 5%, to compare the proportion of TRD and non-TRD patients suffering from comorbidities as well as the proportions that required use of resources such as psychotherapy sessions or psychiatrist visits.

- The duration of a LOT in TRD episodes was lower than for drug-treated non-TRD episodes, suggesting more frequent changes of regimens (Table 4).

Table 4. Duration of Each Line of Treatment by Type of Episode

Line of Treatment	TRD episodes		Non-TRD episodes with at least one ADAP prescription	
	Median duration (days)	Mean duration (days)	Median duration (days)	Mean duration (days)
LOT 1	86 (50 – 121)	201	95 (40 – 246)	227
LOT 2	58 (43 – 113)	138	63 (40 – 155)	178
LOT 3	73 (45 – 196)	201	161 (60 – 413)	350
LOT 4	78 (47 – 210)	218	100 (56 – 290)	277
LOT 5	90 (49 – 271)	251	161 (60 – 472)	381
LOT 6	85 (49 – 263)	242	104 (56 – 308)	291
LOT 7	95 (51 – 287)	266	178 (65 – 458)	306
LOT 8	82 (49 – 231)	231	99 (56 – 243)	234
LOT 9	88 (50 – 268)	252	168 (62 – 433)	368
LOT 10	80 (45 – 203)	193	120 (56 – 441)	278

- Use of combination drug regimens was seen in 46.6% of TRD episodes compared with 12.8% of drug-treated non-TRD episodes ( $P < 0.05$ ).
- A greater proportion of TRD patients suffered from co-morbidities than did non-TRD patients ( $P < 0.05$  in each case below):
  - Anxiety and panic disorder: 50.0% vs 32.7% of TRD and non-TRD patients, respectively.
  - Fatigue: 9.0% vs 5.4% of TRD and non-TRD patients, respectively.
  - Weight loss: 7.6% vs 4.7% of TRD and non-TRD patients, respectively.
  - Sexual dysfunction: 5.3% vs 3.4% of TRD and non-TRD patients, respectively.
  - Suicide: 6.3% vs 3.3% of TRD and non-TRD patients, respectively.
  - Epilepsy: 3.1% vs 1.5% of TRD and non-TRD patients, respectively.
  - Drug/substance abuse: 0.3% vs 0.1% of TRD and non-TRD patients, respectively.
- Patients experiencing TRD episodes underwent 4 times as many sessions of psychotherapy/cognitive behavioral therapy per episode than those experiencing non-TRD episodes (mean number of sessions: 0.047 in TRD episodes vs 0.011 in non-TRD episodes; ratio: 4.3) ( $P < 0.05$ ).
- A greater proportion of patients with at least one TRD episode (17 patients; 0.273%) underwent electroconvulsive therapy than did non-TRD patients (23 patients; 0.023%) ( $P < 0.05$ ).
- Psychiatrist visits by patients with TRD were more than five times higher than those by non-TRD patients (mean number of visits per TRD episode was 0.54 vs 0.10 per non-TRD episode with at least one ADAP prescription) ( $P < 0.05$ ). This was attributable partly to the longer duration of TRD episodes and partly to the higher rate of visits.

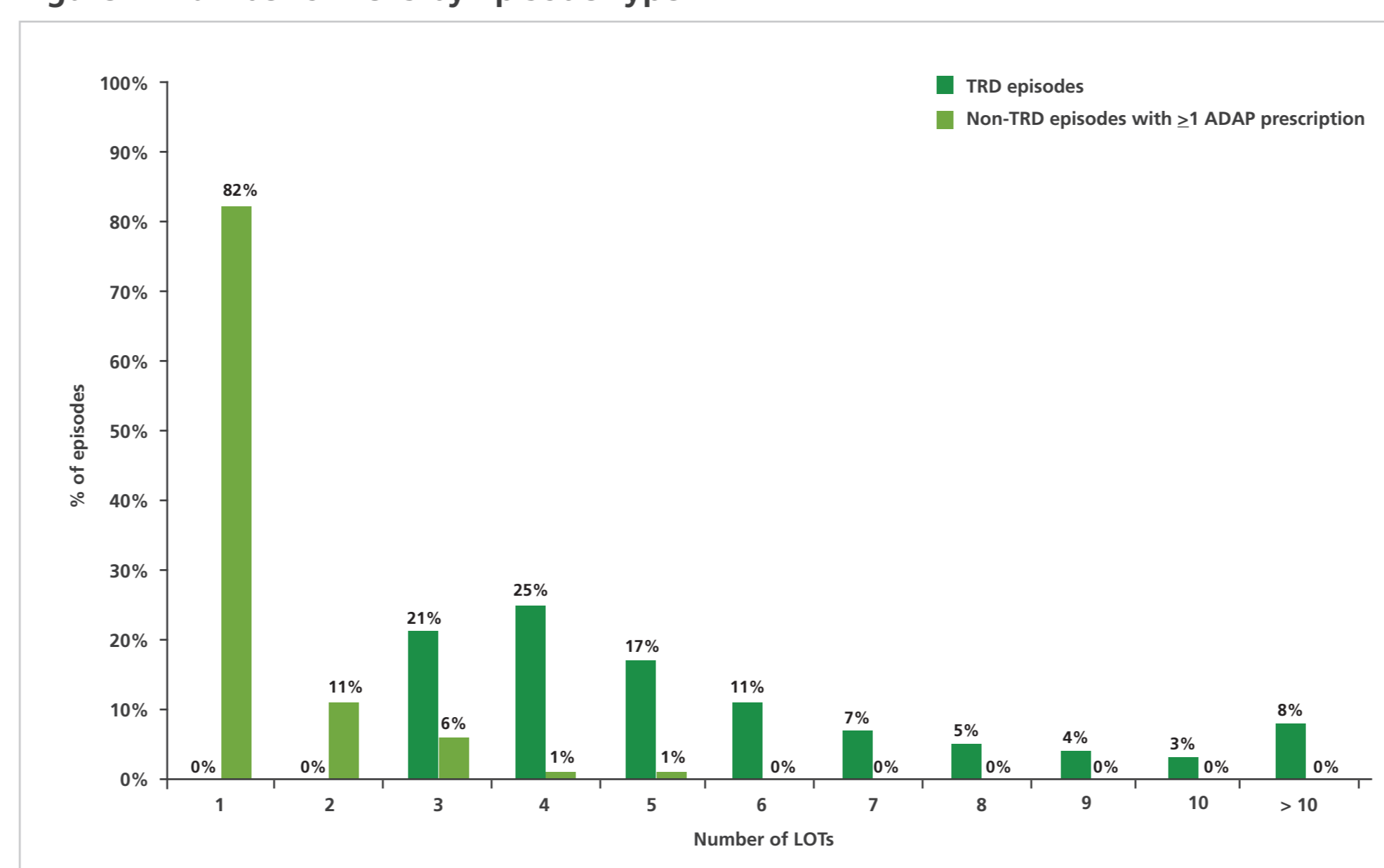
Table 3. Median and Mean Durations of Episodes (In Days)

Episode Number	TRD	Non-TRD episodes with at least one ADAP prescription	All non-TRD episodes
<b>Median duration</b>			
1	889 (486 – 1730)	211 (127 – 388)	148 (120 – 304)
2	873 (481 – 1585)	218 (132 – 407)	175 (120 – 341)
3	785 (462 – 1476)	213 (122 – 393)	177 (120 – 339)
4	1008 (605 – 1548)	204 (120 – 362)	170 (120 – 309)
5	651 (436 – 903)	218 (120 – 367)	183 (120 – 334)
All episodes	883 (485 – 1690)	211 (127 – 391)	152 (120 – 310)
<b>Mean duration</b>			
1	1264	369	303
2	1156	369	319
3	1089	351	312
4	1102	335	295
5	836	323	287
All episodes	1239	368	305

ADAP, anti-depressant and anti-psychotic/anti-manic drugs; TRD, treatment-resistant depression

- While almost half (46%) of all TRD episodes had up to four LOTs, less than a fifth (19%) of non-TRD episodes with one or more ADAP prescriptions had more than one LOT (Figure 2).

Figure 2. Number of LOTs by Episode Type



\*A non-TRD episode may have ≥2 LOTs/regimens, as there may exist regimens that do not count as failed regimens (they may have successor regimens that are step-downs or are the last regimen of the episode or may have failed previously and this already has been counted as a failed regimen – see definition of TRD in the methods section)  
ADAP, anti-depressant and anti-psychotic/anti-manic drugs; TRD, treatment-resistant depression

## CONCLUSION

This analysis of data from the largest provider of health care in the United Kingdom highlights the significant burden of TRD on both patients and providers.

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