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**RESEARCH Open Access**

[](http://crossmark.crossref.org/dialog/?doi=10.1186/s12888-022-04184-8&domain=pdf)Epidemiology of treatment resistant depression among major depressive disorder patients in Israel

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# Abstract

**Introduction:** Major depressive disorder (MDD) is one of the most common mental disorders worldwide, estimated to affect 10–15% of the population per year. Treatment resistant depression (TRD) is estimated to affect a third of these patients who show difficulties in social and occupational function, decline of physical health, suicidal thoughts and increased health care utilization. We describe the prevalence of MDD, TRD and associated healthcare resource utilization in Maccabi Healthcare Services (MHS), a 2.5 million‑member state‑mandated health service in Israel.

**Methods:** All MHS members with an MDD diagnosis were identified within the years 2017–2018 and prevalence assessed by age, sex and TRD. To assess the incidence of MDD, members aged 18–65 years at the start of any MDD episode were identified between 1st January 2016 and 31st May 2018 with at least one systemic first‑line antidepres‑ sant treatment within three months before or after the initial episode. Treatment patterns, time on first‑line treatment, and healthcare resource utilization were compared by TRD.

**Results:** A total of 4960 eligible MDD patients were identified (median age = 51 years, 65% female), representing a period prevalence of 0.218%, and of those, a high proportion of patients received drug treatment (92%). Among incident MDD cases (*n* = 2553), 24.4% had TRD. Factors associated with TRD included increasing age and personal‑

ity disorder. Median time on treatment was 3.7 months (longer for those without TRD than those with) and 81.9% of patients purchased more than one month’s supply of therapy. In the year after index, patients with TRD had a signifi‑ cant increased number of visits to primary care physicians, psychiatrists, emergency room visits, general hospitaliza‑ tions, and psychiatric hospitalizations.

**Conclusion:** Our study shows that prevalence of MDD in Israel is low compared to other countries, however once diagnosed, patients’ are likely to receive drug treatment. Among patients diagnosed with MDD, the proportion of TRD is similar to other countries, increases with age and is associated with increased healthcare utilization, therefore should be a focus of continued research for finding effective long term treatment options.

**Keywords:** Major depressive disorder, Treatment resistant depression, Real‑world retrospective database study

# Introduction

Clinical depression or Major Depressive Disorder (MDD)

is one of the most common mental disorders worldwide,

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accounting for 4.4% of the disease burden worldwide and 7.2% in the European Union [[1](#_bookmark9)–[3](#_bookmark11)]. Prevalence rates vary by age, with women more commonly affected than men

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[[4](#_bookmark12), [5](#_bookmark13)] and lifetime rates varying by country, between 1% in the Czech Republic and 16.9% in the United States of America [[2](#_bookmark10)]. MDD has substantial impact on over- all functioning and quality of life, associated with high comorbidity [[6](#_bookmark14)] and a high burden upon healthcare ser- vices [[7](#_bookmark15)]. By the year 2020, depression was second in the ranking of Disability Adjusted Life Years (DALY) calcu- lated for all ages. MDD has a chronic or recurrent course, characterized by depressive episodes that can last on average for a year, but can also cause disability between episodes [[8](#_bookmark16)].

Clinical guidelines recommend treatment with an anti- depressant medication for 6–12 weeks in the initial acute phase for a first episode and 4–9 months of continued treatment after this period. Patients may require fur- ther maintenance therapy and long term management, switching to a different drug or combination therapy depending on response and severity of the depressive episode [[9](#_bookmark17), [10](#_bookmark18)].

It is estimated that 30%–40% of patients with MDD do not respond to typical antidepressant medications [[11](#_bookmark19)], showing treatment resistant symptoms and failure to achieve remission, with difficulties in social and occu- pational function, decline of physical and mental health, suicidal thoughts [[12](#_bookmark20)] and lower quality of life [[1](#_bookmark9), [7](#_bookmark15), [12](#_bookmark20)]. Treatment resistant depression (TRD) is associated with increased health care utilization and cost with at least 12% more outpatient visits, increased use of psychotropic medications and double the risk of hospitalization than other patients suffering from MDD [[13](#_bookmark21)].

There is no definitive definition for TRD. The most common definition requires a minimum of two prior treatment failures for adequate dose and adequate dura- tion in a current episode [[14](#_bookmark22)–[16](#_bookmark24)], and further defined as a failure to respond to two adequate trials of differ- ent antidepressants given for 6–8 weeks at adequate doses [[17](#_bookmark25), [18](#_bookmark26)]. Other definitions exist including failure to achieve remission to at least one, three or five antidepres- sant drugs [[19](#_bookmark27)–[21](#_bookmark28)], or a staging system which includes failure of different numbers of antidepressant drugs and electroconvulsive therapy (ECT) [[1](#_bookmark9), [15](#_bookmark23), [22](#_bookmark29)].TRD preva- lence estimates vary widely dependent on the definition used, from 35% in a study limited to subjects with a MDD diagnosis [[23](#_bookmark30)] to less than 10% in a study that included a wider range of depression diagnoses among subjects [[24](#_bookmark31)]. A real world study in primary care found a prevalence rate of 22% among 1212 patients with MDD [[25](#_bookmark32)]. Studies have shown that TRD response rates are poor, with one study showing a 10% one-year response rate to standard MDD treatments [[26](#_bookmark33)]. Other therapies that can be tried include ECT, repetitive transcranial magnetic stimula- tion, intravenous/intranasal ketamine, inhaled nitrous oxide, vagus nerve stimulation, deep brain stimulation,

magnetic seizure therapy and buprenorphine, and also psychosocial and cultural therapies [[1](#_bookmark9)].

We describe here a retrospective cohort study of the epidemiology, characteristics, treatment patterns and healthcare resource utilization of patients with MDD in Israel.

# Methods

**Data source**

This retrospective cohort study was conducted using the computerized databases of Maccabi Healthcare Services (MHS), a state-mandated insurer-provider with 2.5 mil- lion members, representing a quarter of the population in Israel, and shares similar sociodemographic char- acteristics with the general population [[27](#_bookmark34)]. The MHS database contains longitudinal data that are automati- cally collected since 1993 for a stable population people (with less than 1% of members moving out each year), including diagnosis data, laboratory results from a single central laboratory, pharmacy prescription and purchase data, hospitalizations, procedures and consultations. MHS uses the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) cod- ing systems, as well as self-developed coding systems to provide more granular diagnostic information. Proce- dures are coded using *Current Procedural Terminology* (CPT) codes.

**Study population**

Two separate study cohorts were analyzed in this study:

***Period prevalence cohort***

In this retrospective cohort study the period prevalence was assessed among all MHS members with at least one MDD ICD-9-CM diagnosis code (296.2, 296.3 or 296.35) from a psychiatrist or general physician for the period 2017–2018 (to allow for an episode of up to a year). This cohort consisted of all patients with a diagnosis code, whether they received treatment or not.

***Incidence cohort***

We identified MHS members aged 18 to 65 years with the start of any MDD episode (main study cohort) between 1st January 2016 and 31st May 2018 (with a minimum of one year of follow up). The start of a `MDD episode was defined as an ICD-9-CM diagnosis code in the medical notes with a gap of at least one year to a previous diag- nosis [[28](#_bookmark35)]. To be included in this incident study cohort, patients had to have received at least one systemic first- line (L1) therapy for MDD. Index date was set as the date of L1 antidepressant treatment initiation within 3 months before or after MDD episode start date. Patients with

less than one year of healthcare registration in MHS or

a diagnosis of schizophrenia or bipolar disease before index date were excluded.

A sub-analysis was performed for patients with the same inclusion/exclusion criteria, but for those with a first ever recorded MDD episode within the MHS system.

**Study variables**

Demographic and clinical data collected included age at index date, sex, socioeconomic status (SES), residence area, prevalence of comorbid conditions, body mass index (BMI) and smoking. SES was categorized into quartiles based on the poverty index of the member’s enumeration area, as defined by 2008 National Census [[29](#_bookmark36)]. The poverty index is based on several parameters including, household income, educational level, crowd- ing, physical conditions, and car ownership. Smoking data were collected from physician reporting and classi- fied into ever, never or unknown.

Baseline chronic diseases were identified using vali- dated MHS registries, (for diabetes mellitus [[30](#_bookmark37)], hyper- tension [[31](#_bookmark38)], chronic obstructive pulmonary disease [COPD], cardiovascular disease [[32](#_bookmark39)], hypertension, oste- oporosis [[33](#_bookmark40)], cancer [[34](#_bookmark41)]) or by two or more ICD-9-CM diagnosis codes before index date on separate physician appointments for postpartum depression, anxiety, panic disorder, personality disorder and social phobia. The reg- istries were developed in order to improve the quality of chronic care delivery to its members and are continu- ously updated, and identify patients via automatic search formulas, as opposed to being dependent upon active reporting by physicians. Cancer history was obtained from the National Cancer Registry which uses diagno- ses linked to pathology reports and cross referenced with cancer medication approvals in MHS. In addi- tion, comorbidity was measured by the Deyo-Charlson Comorbidity Index [[35](#_bookmark42)] and augmented using the MHS chronic disease registries. All comorbidities were meas- ured in the one-year pre-index period. Healthcare ser- vices utilization included primary care physician (PCP) visits, hospitalizations (number and duration), emer- gency room (ER) visits and ECT therapy.

**Treatment patterns**

Treatment lines (L1-3) were defined at the patient level according to the sequence of dispensed medication. Anti- depressant drugs were grouped into selective seroto- nin reuptake inhibitors (SSRI) monotherapy, other drug monotherapy (serotonin and noradrenaline reuptake inhibitors; monoamine oxidase inhibitors; atypical anti- depressants including venlafaxine, duloxetine, vortioxe- tine, bupropion, mirtazapine, milnacipran), combination therapy (any combination of at least two medications) and tricyclic antidepressants (TCA) monotherapy.

Addition of a new drug to a current regimen was con- sidered a new treatment line, and cessation of a medica- tion from a combination regimen (likely due to tolerance issues) was considered the same line.

TRD was defined by purchase of at least three lines of treatment within the first 12 months after index date. Type of L1 antidepressant use within the MDD cohort and time on treatment were determined.

**Statistical analysis**

Descriptive analyses were conducted to compare the demographic, clinical and treatment characteristics for the study cohort for those with and without TRD in the one-year period following index date. Categorical vari- ables were reported as frequency and percentage and compared using chi-square testing, and continuous vari- ables were reported as mean (standard deviation [SD]) or median (interquartile range [IQR]) and compared using the t-test.

Backward logistic regression was used to compute adjusted odds ratios and 95% confidence intervals (CI) for the explanatory variables for factors associated with TRD.

Treatment duration was assessed using Kaplan–Meier analysis, and median time on treatment with 95% CI pre- sented. Discontinuation was defined as at least 90 days’ survival after run out of last treatment or line switch.

All analyses were conducted using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp, or R version 3.5.1, and a *P* value < 0.05 was considered statisti- cally significant.

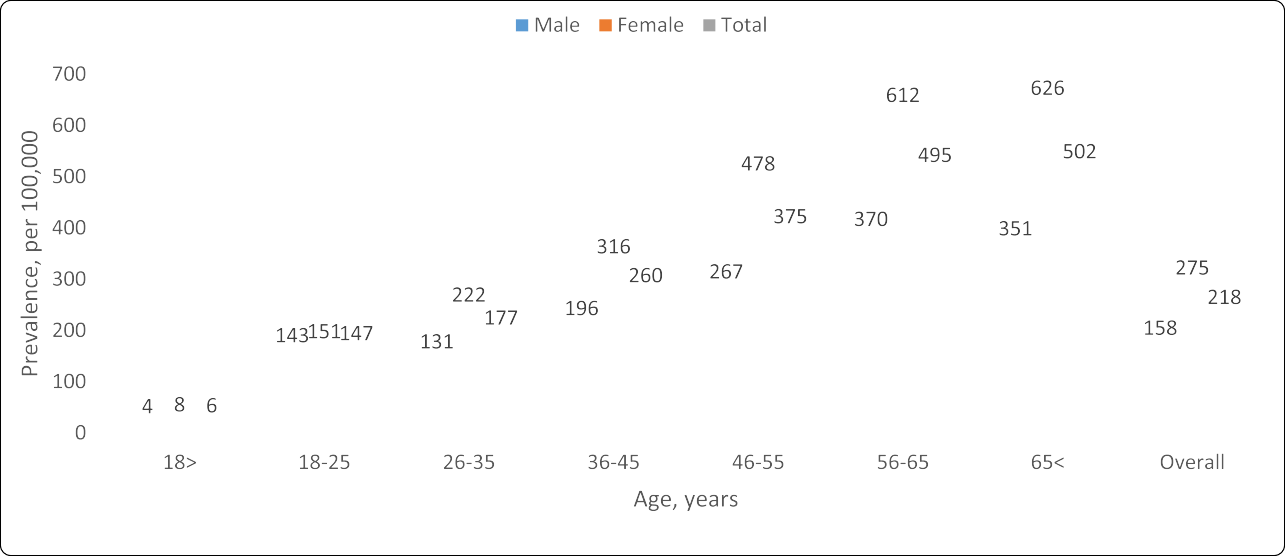
The study was approved by the local ethics review board of MHS in Israel.

# Results

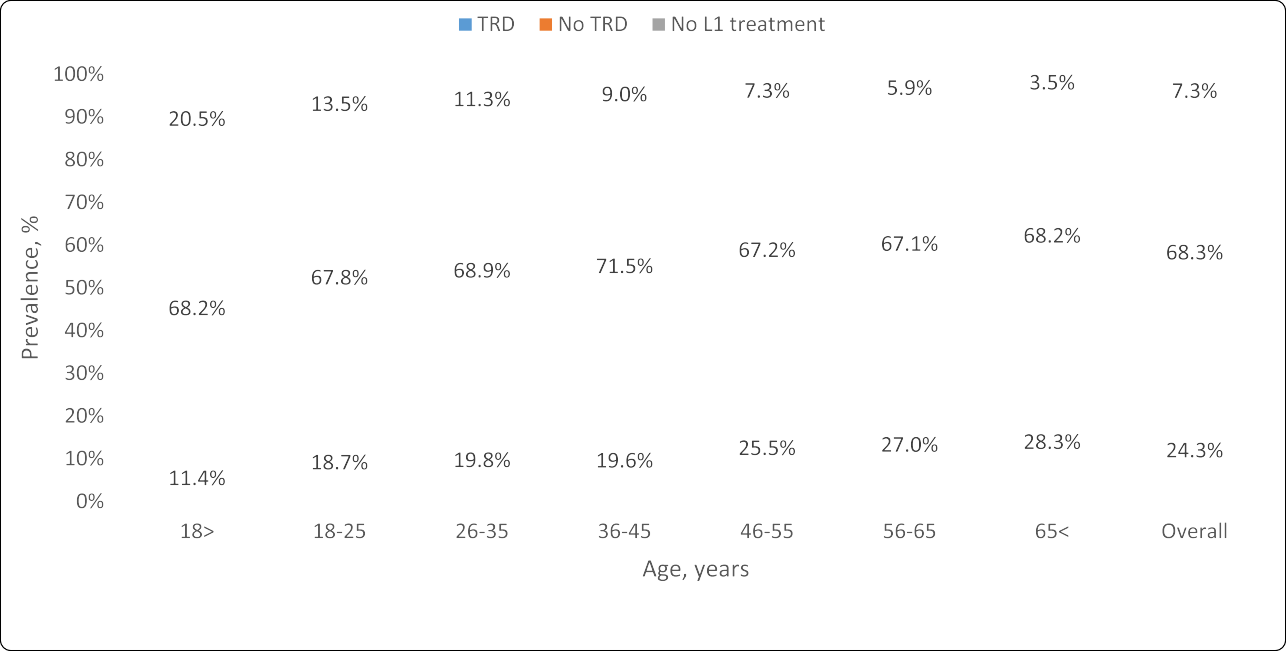
**Period prevalence cohort**

A total of 4960 patients had a prevalent MDD episode in the prevalence period (2018). The number of patients with MDD increased with age (median age was 51 years, IQR 38–63) and 65% were female (Fig. [1](#_bookmark0)). Overall prevalence of MDD in MHS was 0.218%. When weight adjusted according to the WHO standard world popula- tion, prevalence was 0.202% (data not shown).

Among those diagnosed, mean TRD was 24.3%, and the proportion of the cohort with TRD increased with age (11.4% for age < 18 years to 28.3% for age > 65 years, Fig. [2](#_bookmark1)). In addition, 92.7% of patients were treated with L1 therapy. Figure [3](#_bookmark2) shows distribution of L1 treatment by age, with SSRI being the drug of choice for under 18 year olds (91.4%), with use declining to 41.2% for patients over the age of 65 years.



**Fig. 1** Age‑specific period prevalence of patients with major depressive disorder by sex for the period 2017–2018, per 100,000 population, *n* = 4960



**Fig. 2** Age‑specific period prevalence of all patients with major depressive disorder by treatment resistant depression for the period 2017–2018, by relative distribution of the prevalent cohort, *n* = 4960. TRD, treatment resistant depression; L1, first‑line treatment

**Incidence cohort**

A total of 2553 patients had a new MDD episode in the study period (1/1/2016–31/5/2018) and initiated drug treatment. Of these, 24.4% had TRD according to the definition we used, and 68.1% had a first ever recorded MDD episode.

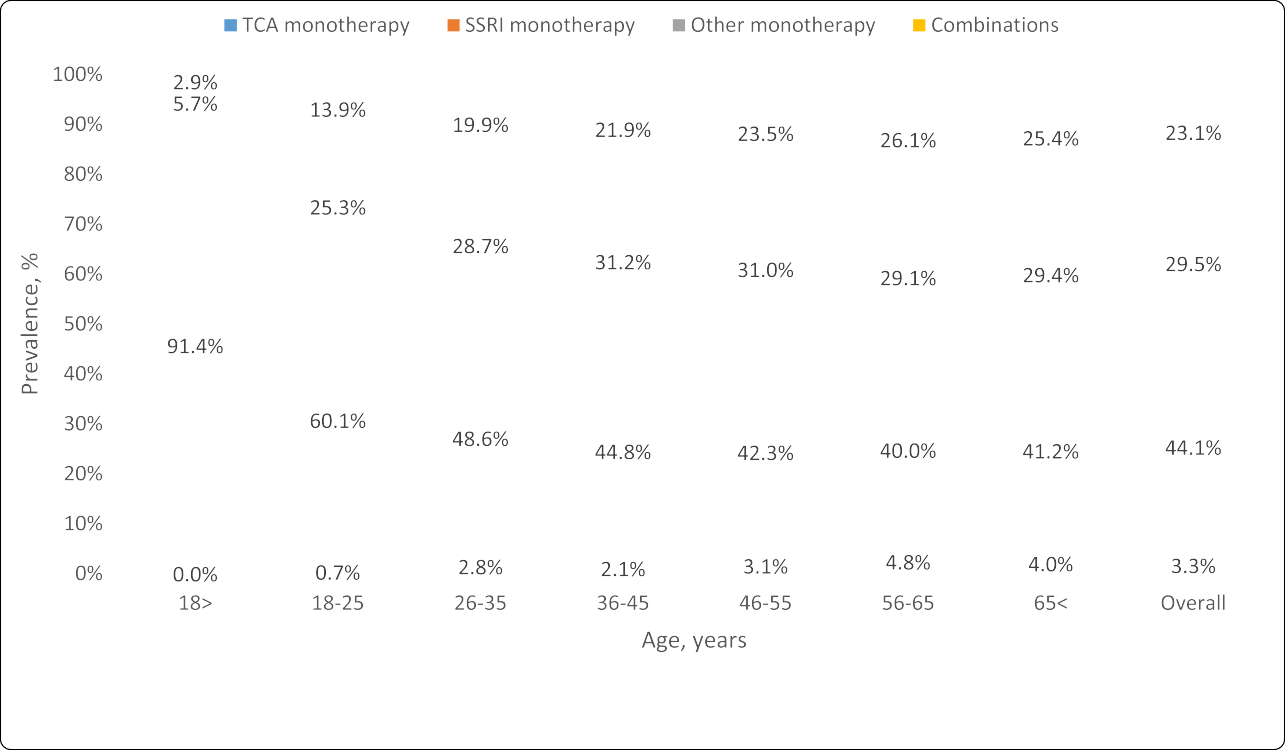
Median age at start of treatment was 47 years (IQR 36–56), 64.4% were female, 21.6% had hyperten-

sion, 11.1% had diabetes, 24.4% had anxiety, 6.1% had

personality disorder and 48.9% were past or present smokers (Table [1](#_bookmark3)).

Factors associated with TRD included increasing age, suffering from personality disorder and not living in the northern region of the country (Table [2](#_bookmark4)).

A total of 81.9% of patients purchased more than one month’s supply of treatment: 79.8% of those that pur- chased SSRI monotherapy, 95.1% of those that purchased combination therapy and 62.7% of those that purchased



**Fig. 3** Age‑specific period prevalence of patients with major depressive disorder by first‑line treatment for those who received treatment for the period 2017–2018, by relative distribution of the prevalent cohort, *n* = 4596. TCA, tricyclic antidepressants; SSRI, selective serotonin reuptake inhibitors

TCA monotherapy. Of those with TRD, 80.1% purchased more than one month’s supply of treatment (as compared to 82.4% without TRD): 72.0% of those that purchased SSRI monotherapy, 96.2% of those that purchased com- bination therapy and 73.9% of those that purchased TCA monotherapy (Table [3](#_bookmark5)). Median time on L1 treatment was 3.78 months for SSRI monotherapy, 4.11 months for combination therapy and 2.17 months for TCA mono- therapy (Table [4](#_bookmark6), Fig. [4](#_bookmark7)). For patients with no TRD, those that received L1 combination therapy or SSRI mono- therapy had a longer median L1 time on treatment (9.50 [7.63, 10.65], 7.27 [6.08, 8.61] respectively) than those that received L1 other treatment or TCA (5.23 [4.24, 7.1], 2.25 [0.99, 8.12], respectively, *P* = 0.091). For patients with TRD, there was no difference in their time on treat- ment between different L1 therapies (*P* = 0.20).

In the year after index, patients with TRD had an increased number of PCP visits, psychiatrist visits, ER visits, general hospitalizations and psychiatric hospitali- zations (Table [5](#_bookmark8)).

A sub-analysis performed on a cohort of patients with a first ever MDD episode showed similar results.

# Discussion

**Period prevalence cohort**

Major depressive disorder is a severe disorder that had an average global prevalence in 2010 of 6% [[2](#_bookmark10)], with a

recent systemic review reporting lifetime prevalence of between 2 and 21% [[36](#_bookmark43)]. Approximately 6.7% of adults over the age of 18 had a major depressive episode in the US in 2015 [[37](#_bookmark44), [38](#_bookmark45)] which increased to 8.4% in 2020 [[39](#_bookmark46)]. Prevalence rate found in our study was very low compared to published rates around the world [[40](#_bookmark47)] and also compared to the World Health Organization World Mental Health Study which found a prevalence in Israel of 5.9% [[41](#_bookmark48)]. In 2007 a process to transfer responsibility of mental health services from the Ministry of Health to the health funds (MHS is one of four health funds in Israel) was initiated and took effect in July 2015. There- fore the low prevalence rate found in our study could be due to the fact that even though the responsibility for mental health patients passed to the health funds, many patients with MDD were still treated in out-patient clin- ics of psychiatric hospitals (not associated with the health funds), and their diagnoses did not reach the MHS health fund’s databases during our study period. In addition, this low rate found in the MHS database could be due to under reporting and under diagnosis by physicians. A lit- erature review on depression diagnosis in primary care in Israel described the challenges that need to be overcome in order to provide better care to these patients [[42](#_bookmark49)]. The authors describe a prevalence of MDD of 1.6–5.9%, associated with female sex and fewer years of educa- tion. They describe how many cases were undiagnosed

**Table 1** Demographic and clinical characteristics of the incident study cohort (patients with the start of any major depressive disorder episode within the study period, 1/1/2016–31/5/2018) at treatment initiation, *n* = 2553

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Patient characteristics** |  | **Patients without TRD (*N*** = **1929, 75.6%)** | **Patients with TRD (*N*** = **624, 24.4%)** | **Total (*N*** = **2553)** | ***P*-value** |
| Age, y | Median (IQR) | 46 (35, 55) | 49 (38, 56) | 47 (36, 56) | 0.001 |
| Sex | Male | 672 (34.8%) | 237 (38.0%) | 909 (35.6%) | 0.154 |
|  | Female | 1257 (65.2%) | 387 (62.0%) | 1644 (64.4%) |  |
| Socio‑economic status | Low | 581 (30.1%) | 188 (30.1%) | 769 (30.1%) | 0.711 |
|  | Medium | 402 (20.8%) | 121 (19.4%) | 523 (20.5%) |  |
|  | High | 946 (49.0%) | 315 (50.5%) | 1261 (49.4%) |  |
| District | Central | 1348 (69.9%) | 472 (75.6%) | 1820 (71.3%) | 0.021 |
|  | North | 403 (20.9%) | 104 (16.7%) | 507 (19.9%) |  |
|  | South | 178 (9.2%) | 48 (7.7%) | 226 (8.9%) |  |
| Comorbidities | Deyo‑Charlson co‑morbidity index, mean (SD) | 0.88 (1.55) | 0.90 (1.47) | 0.89 (1.53) | 0.788 |
|  | Diabetes mellitus | 207 (10.7%) | 76 (12.2%) | 283 (11.1%) | 0.316 |
|  | Cardio‑vascular disease | 157 (8.1%) | 65 (10.4%) | 222 (8.7%) | 0.079 |
|  | Hypertension | 395 (20.5%) | 157 (25.2%) | 552 (21.6%) | 0.014 |
|  | Chronic obstructive pulmonary disease | 50 (2.6%) | 21 (3.4%) | 71 (2.8%) | 0.307 |
|  | Cancer | 141 (7.3%) | 46 (7.4%) | 187 (7.3%) | 0.959 |
|  | Osteoporosis | 108 (5.6%) | 43 (6.9%) | 151 (5.9%) | 0.234 |
| Other co‑morbidities \* | Post‑partum depression | 5 (0.3%) | 0 (0.0%) | 5 (0.2%) | 0.203 |
|  | Anxiety | 460 (23.8%) | 162 (26.0%) | 622 (24.4%) | 0.285 |
|  | Panic attacks | 72 (3.7%) | 16 (2.6%) | 88 (3.4%) | 0.241 |
|  | Personality disorder | 103 (5.3%) | 52 (8.3%) | 155 (6.1%) | 0.006 |
|  | Social phobia | 16 (0.8%) | 7 (1.1%) | 23 (0.9%) | 0.502 |
| Smoking | Ever | 926 (48.2%) | 319 (51.1%) | 1245 (48.9%) | 0.324 |
|  | Never | 995 (51.7%) | 305 (48.9%) | 1300 (51.0%) |  |
|  | Missing | 2 (0.1%) | 0 (0.0%) | 2 (0.1%) |  |
| Body mass index \*\* | Mean (SD) | 26.54 (5.6) | 26.66 (5.59) | 26.57 (5.6) | 0.635 |

\* within 1 year prior to index date

\*\* for those with a BMI measurement closest within 5 years before index date, *n* = 2374 (93.3%)

*TRD* treatment resistant depression

**Table 2** Multivariable model (adjusted odds ratios) for factors associated with treatment resistant depression within one year from index date for the incident study cohort (patients with the start of any major depressive disorder episode within the study period, 1/1/2016–31/5/2018), *n* = 2553

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | | **Adjusted OR** | **95% CI** |  | ***P*-value** |
|  | **Lower** | **Upper** |  |
| Age | per year | 1.014 | 1.006 | 1.021 | < 0.001 |
| Sex | Female vs. Male | 0.889 | 0.736 | 1.074 | 0.222 |
| Socio‑economic status | Low (ref.) |  |  |  |  |
|  | Medium | 0.893 | 0.684 | 1.166 | 0.406 |
|  | High | 0.939 | 0.754 | 1.169 | 0.572 |
| District | Centre (ref.) |  |  |  |  |
|  | North | 0.695 | 0.543 | 0.889 | 0.004 |
|  | South | 0.758 | 0.535 | 1.074 | 0.119 |
| Personality disorder | Yes vs. no | 1.706 | 1.201 | 2.424 | 0.003 |
| *CI* confidence intervals |  |  |  |  |  |

**Table 3** Medication purchases by type of antidepressant medication for one month or more, by treatment resistant depression, for the incident study cohort (patients with the start of any major depressive disorder episode within the study period, 1/1/2016– 31/5/2018), *n* = 2553

**Patients without TRD (*N* = 1929, 75.6%)**

**Patients with TRD (*N* = 624, 24.4%)**

**Total (*N* = 2553)**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **N** | **%** |  | **N** | **%** |  | **N** | **%** |
| **SSRI monotherapy** | Single purchase | 163 | 17.9% |  | 75 | 28.0% |  | 238 | 20.2% |
|  | > 1 purchase | 748 | 82.1% |  | 193 | 72.0% |  | 941 | 79.8% |
|  | **Total** | **911** | **100.0%** |  | **268** | **100.0%** |  | **1179** | **100.0%** |
| **Other monotherapy** | Single purchase | 133 | 23.2% |  | 37 | 20.9% |  | 170 | 22.7% |
|  | > 1 purchase | 440 | 76.8% |  | 140 | 79.1% |  | 580 | 77.3% |
|  | **Total** | **573** | **100.0%** |  | **177** | **100.0%** |  | **750** | **100.0%** |
| **Combination therapy** | Single purchase | 21 | 5.3% |  | 6 | 3.8% |  | 27 | 4.9% |
|  | > 1 purchase | 372 | 94.7% |  | 150 | 96.2% |  | 522 | 95.1% |
|  | **Total** | **393** | **100.0%** |  | **156** | **100.0%** |  | **549** | **100.0%** |
| **TCA monotherapy** | Single purchase | 22 | 42.3% |  | 6 | 26.1% |  | 28 | 37.3% |
|  | > 1 purchase | 30 | 57.7% |  | 17 | 73.9% |  | 47 | 62.7% |
|  | **Total** | **52** | **100.0%** |  | **23** | **100.0%** |  | **75** | **100.0%** |
| **Total** | Single purchase | 339 | 17.6% |  | 124 | 19.9% |  | 463 | 18.1% |
|  | > 1 purchase | 1590 | 82.4% |  | 500 | 80.1% |  | 2090 | 81.9% |
|  | **Total** | **1929** | **100.0%** |  | **624** | **100.0%** |  | **2553** | **100.0%** |

(Other monotherapy comprised: 39.1% venlafaxine, 21.5% duloxetine, 10.1% vortioxetine, 9.2% bupropion, 8.4% mirtazapine, 3.9% milnacipran)

*TRD* treatment resistant depression, *TCA* tricyclic antidepressants, *SSRI* selective serotonin reuptake inhibitors

**Table 4** Time on treatment (months) of L1 treatment using Kaplan–Meier analysis, for the incident study cohort (patients with the start of any major depressive disorder episode within the study period, 1/1/2016–31/5/2018), *n* = 2553

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **L1 treatment** | **TRD** | **N** | **Number (%) discontinued** | **Median time on treatment (95% CI), months** | **% on treatment at 3 months** | **% on treatment at 6 months** | **% on treatment at 12 months** | **Log rank P value** |
| **SSRI mono-** | No TRD | 911 | 884 (97.04%) | 7.27 (6.08, 8.61) | 65.2% | 53.4% | 25.7% | < 0.0001 |
| **therapy** | TRD | 268 | 268 (100.00%) | 2.04 (1.87, 2.27) | 22.0% | 4.5% | 0.0% |  |
|  | **Total** | **1179** | **1152 (97.71%)** | **3.78 (3.32, 4.67)** | **55.3%** | **42.2%** | **19.8%** |  |
| **Other mono-** | No TRD | 573 | 554 (96.68%) | 5.23 (4.24, 7.1) | 60.4% | 48.2% | 27.2% | < 0.0001 |
| **therapy** | TRD | 177 | 177 (100.00%) | 2.07 (1.91, 2.33) | 28.3% | 7.9% | 0.0% |  |
|  | **Total** | **750** | **731 (97.47%)** | **3.22 (2.96, 3.95)** | **52.8%** | **38.7%** | **20.8%** |  |
| **Combination** | No TRD | 393 | 376 (95.67%) | 9.50 (7.63, 10.65) | 70.2% | 58.7% | 31.6% | < 0.0001 |
| **therapy** | TRD | 156 | 156 (100.00%) | 2.32 (2.01, 2.63) | 30.1% | 6.4% | 0.0% |  |
|  | **Total** | **549** | **532 (96.90%)** | **4.11 (3.48, 5.26)** | **58.8%** | **43.8%** | **22.6%** |  |
| **TCA monother-** | No TRD | 52 | 52 (100.00%) | 2.25 (0.99, 8.12) | 42.3% | 36.5% | 21.2% | 0.013 |
| **apy** | TRD | 23 | 23 (100.00%) | 1.91 (1.18, 3.48) | 30.4% | 4.4% | 0.0% |  |
|  | **Total** | **75** | **75 (100.00%)** | **2.17 (1.05, 3.32)** | **38.7%** | **26.7%** | **14.7%** |  |
| **Overall** | No TRD | 1929 | 1866 (96.73%) | 6.97 (6.12, 8.19) | 64.1% | 52.5% | 27.2% | < 0.0001 |
|  | TRD | 624 | 624 (100.00%) | 2.07 (1.97, 2.27) | 26.1% | 5.9% | 0.0% |  |
|  | **Total** | **2553** | **2490 (97.53%)** | **3.65 (3.29, 3.98)** | **54.8%** | **41.1%** | **20.5%** |  |

(Other monotherapy comprised: 39.1% venlafaxine, 21.5% duloxetine, 10.1% vortioxetine, 9.2% bupropion, 8.4% mirtazapine, 3.9% milnacipran)

*TRD* treatment resistant depression, *SSRI* selective serotonin reuptake inhibitors, *TCA* tricyclic antidepressants

and how most patients had persistent depression or achieved only partial remission. The Israeli population consists of a rich variety of cultural backgrounds, beliefs

and languages, and many immigrant populations. Immi- grants are known to be at high risk of depression [[43](#_bookmark50)] and communication limitations may make diagnosis and

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| TCA | 75 (0) | 29 (46) | 20 (55) | 16 (59) | 11 (64) | 0 (75) |
| SSRI | 1179 (0) | 651 (526) | 497 (680) | 418 (759) | 232 (942) | 0 (1152) |
| Other | 750 (0) | 396 (354) | 289 (460) | 248 (501) | 155 (593) | 0 (731) |
| Combination | 549 (0) | 322 (226) | 239 (308) | 204 (342) | 122 (423) | 0 (532) |

**T****able 5** Healthcare resource utilization for one year after index date for patients in the incident study cohort (patients with the start of any major depressive disorder episode within the study period, 1/1/2016–31/5/2018) by treatment resistant depression, *n* = 2553

Strata  ~~+~~ TCA  ~~+~~ SSRI  ~~+~~ Other  ~~+~~ Combination

100%

75%

+

++

50%

+

+

+

+

25%

++ ++

+**+**+++**+**

++++

0%

p = 0.042

0

+++

**+**

3

6

9

12

15

Follow up time, months

Number at risk (number of events)

**Fig. 4** Time on treatment (months) on first‑line treatment for patients in the incident study cohort (patients with the start of any major depressive disorder episode within the study period, 1/1/2016–31/5/2018), *n* = 2553. (Other monotherapy comprised: 39.1% venlafaxine, 21.5% duloxetine, 10.1% vortioxetine, 9.2% bupropion, 8.4% mirtazapine, 3.9% milnacipran). *TCA* tricyclic antidepressants, *SSRI* selective serotonin reuptake inhibitors

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | | **Patients without TRD (*N*** = **1929,** | **Patients with TRD (*N*** = **624,** | **Total *(n*** = **2553)** | ***P*-value** |
| **75.6%)** | **24.4%)** |  |  |
| Visits – Primary care physician | ≥ 1, n (%) | 1858 (96.3%) | 613 (98.2%) | 2471 (96.8%) | 0.018 |
|  | Quantity, median (IQR) | 10 (6, 16) | 14 (9, 21) | 11 (7, 17) | < 0.001 |
| Visits—Psychiatrist | ≥ 1, n (%) | 1745 (90.5%) | 600 (96.2%) | 2345 (91.9%) | < 0.001 |
|  | Quantity, median (IQR) | 3 (2, 5) | 6 (3, 9) | 4 (2, 6) | < 0.001 |
| Emergency room visits | ≥ 1, n (%) | 415 (21.5%) | 163 (26.1%) | 578 (22.6%) | 0.017 |
|  | Quantity, median (IQR) | 1 (1, 2) | 1 (1, 2) | 1 (1, 2) | 0.005 |
| Hospitalizations | ≥ 1, n (%) | 262 (13.6%) | 138 (22.1%) | 400 (15.7%) | < 0.001 |
|  | Number of separate hospitalizations, median (IQR) | 1 (1, 2) | 1 (1, 2) | 1 (1, 2) | 0.267 |
|  | Number of nights, *median (IQR)* | 4 (2, 13.5) | 6 (2, 39) | 5 (2, 20) | 0.031 |
| Psychiatric Hospitalizations | ≥ 1, n (%) | 66 (3.4%) | 57 (9.1%) | 123 (4.8%) | < 0.001 |
|  | Number of separate hospitalizations, median (IQR) | 1 (1, 1) | 1 (1, 2) | 1 (1, 2) | 0.031 |
|  | Number of nights, *median (IQR)* | 20 (6, 42) | 40 (10, 67) | 27.5 (8, 61) | 0.279 |
| Electroconvulsive therapy | ≥ 1, n (%) a | 14 (0.7%) | 18 (2.9%) | 32 (1.3%) | < 0.001 |
|  | Time to ECT treatment, *for those that initiated treatment after index date*, median (IQR) | 5.39 (3.12, 18.63) | 10.5 (4.28, 16.95) | 9.99 (3.53, 16.25) | 0.733 |

a excluding those with ECT before index date

*TRD* treatment resistant depression, *ECT* electroconvulsive therapy

treatment challenging. In addition, the stigma of mental illness is still high in Israel and patients may convince their physicians not to report a major depressive diagno- sis in the electronic database [[44](#_bookmark51)], or report less a severe

Cumulative time on treatment

disease diagnosis such as anxiety. The process of transfer of responsibility of mental health services from the Min- istry of Health to the health funds increased the number of patients with MDD that primary care doctors needed

to diagnosis and treat, therefore necessitating specialist knowledge and timely referral to a psychiatrist.

Among patients diagnosed with MDD, nearly one quarter of the incident MDD cases were TRD in line with previous studies [[17](#_bookmark25), [25](#_bookmark32), [45](#_bookmark52), [46](#_bookmark53)]. Another study reported a much higher proportion of TRD, however this was a clinical trial where all patients received medication according to protocol [[8](#_bookmark16)]. TRD increased with age and ranged between 11.4% for under 18 year olds to 28.3% for patients aged over 65 years old. In real-world clinics, not all patients will receive treatment or move to another line of therapy, however we found that untreated patients made up just 3–20% of the entire prevalence cohort (depending on age group and sex), lower than observed in other countries [[41](#_bookmark48)]. This highlights that although the prevalence observed in Israel is lower than other countries, once diagnosed, patients are likely to receive treatment.

**Incidence cohort: Treatment patterns**

Median age in the incidence cohort at index date was 47 years (IQR 36–56), similar to age reported in another retrospective database study [[47](#_bookmark54)].

We found a higher prevalence of MDD amongst women across all age groups, with almost twice as many women than men, confirmed by previous studies [[5](#_bookmark13), [48](#_bookmark55)]. It has been suggested that women present with more depressive symptoms than men, who less frequently meet the diagnostic threshold for a MDD diagnosis. Another theory proposed that men and women have different types of symptoms, with men ascribing depression to work related issues and women ascribing depression to relationship problems. This theory also highlights dif- ferent coping mechanisms with men pursuing sports or drinking alcohol and women using emotional outlets [[49](#_bookmark56)]. However, many structural changes have been tak- ing place over the last few decades as more women join the workforce and share childcare responsibilities, which may influence prevalence of MDD. Another study reports how socioeconomic and family related factors signifi- cantly effect this variation between the sexes, with lower risk of depression associated with marriage or cohabiting with a partner and with higher socioeconomic level [[50](#_bookmark57)].

Our analysis indicates that TRD was significantly asso- ciated with personality disorder. Personality disorder may present as depressive mood, showing an interac- tion between the two disorders [[51](#_bookmark58), [52](#_bookmark59)] and is associated with poor response to treatment [[53](#_bookmark60), [54](#_bookmark61)]. Previous stud- ies have shown that improvement in MDD affects the outcome of personality disorder [[55](#_bookmark62)]. Other factors associated with TRD include older age, marital status, long duration of current MDD episode, anxiety, higher suicidal risk and high numbers of hospitalization [[56](#_bookmark63)].

Residential area was an unexpected factor associated with TRD and is relevant only in the Israeli setting. We suggest that this finding may reflect healthcare disparities since this region has less access to healthcare including mental health professionals and thereby leading to under diagnosis.

SSRIs were the most frequently initiated L1 treatment (46%). A total of 22% received combination therapy, (con- sisting of any combination of at least two antidepressants drugs: 51% SSRI + another antidepressant drug, and 19% combination of two other antidepressants). Whereas there are no clinical trials that recommend combination therapy and the increased effectiveness is debated [[57](#_bookmark64)– [60](#_bookmark65)], there is some evidence to suggest that combination therapy may be effective particularly in the elderly [[61](#_bookmark66)], and the combination of venlafaxine and mirtazapine may be particularly effective in difficult-to-treat depression [[62](#_bookmark67), [63](#_bookmark68)]. Advantages of combination therapy may include rapid response with no titration necessary, however may have disadvantages of adverse reactions and adherence issues.

Our study shows that median time on L1 treatment was

3.6 months and 18% had a single medication purchase only. Guidelines recommend continuing antidepressants for 4 to 9 months after initial symptom resolution, how- ever, many patients discontinue earlier (most within first 3 months) probably due to side effects, lack of efficacy or improvement of symptoms [[64](#_bookmark69)]. TCA treatment was more likely to be discontinued after one month, in line with previous studies that report increased side effects with this therapeutic group [[65](#_bookmark70)] and patients that initi- ated SSRI or combination therapy for L1 with no TRD had longer time on treatment than those that received TCA or other treatment.

Patients with TRD had increased healthcare utiliza- tion including PCP and psychiatry visits, hospitalizations and ER visits, incurring higher burden of disease and healthcare costs as reported in previous studies [[46](#_bookmark53), [66](#_bookmark71)]. A previous study has found that patients suffering from TRD have greater risk of unemployment, reduced work productivity, and poorer patient health-related quality of life compared to responders [[67](#_bookmark72)]. To date, treatment options have been limited, however the treatment land- scape is evolving, and a novel agent esketamine has been approved by the FDA and the Israel Ministry of Health in the last year for patients with MDD and TRD after failure of two previous lines of treatment, allowing for an addi- tional therapeutic approach for these patients.

The strengths of this study include the overall size of the sample and the real-world generalizability of data drawn from a broad claims database in Israel. However, it may have limitations associated with its retrospec- tive cohort design. Data on purchases made outside of

MHS pharmacies were not captured; however, patients are unlikely to buy medications outside of MHS due to their discounted price within MHS. It should also be noted that actual medication use is unknown, as dis- pensed medications may not be consumed. However, previous studies have demonstrated the validity of this approach for measuring compliance with chronic medi- cations [[68](#_bookmark73)].

# Conclusion

Our study shows that prevalence of MDD in Israel is low compared to other countries, however once diagnosed patients are likely to receive drug treatment. Among patients diagnosed with MDD, the proportion of TRD is similar to other countries, increases with age and is asso- ciated with increased healthcare utilization, therefore should be a focus of continued research for finding effec- tive long term treatment options.

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**Authors’ contributions**

Conceptualization and design: SSM, GC, SG, NB, VS, OSR; analysis and interpre‑ tation: SSM, GC, SG, NB, VS, OSR; writing and revising the content: SSM, GC, SG, NB, VS, OSR; final approval: SSM, GC, SG, NB, VS, OSR. All authors have read and agreed to the published version of the manuscript.

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**Availability of data and materials**

The datasets generated and analyzed during the current study are not pub‑ licly available due to restrictions in MHS and the Israel Ministry of Health but are available from the corresponding author on reasonable request.

**Declarations**

**Ethics approval and consent to participate**

The authors state that they have obtained appropriate institutional review board approval and have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. The study was approved by the local ethics review board of Maccabi Healthcare Services

in Israel who waived informed consent due to the anonymous retrospective nature of this database study.

**Consent for publication**

Not applicable.

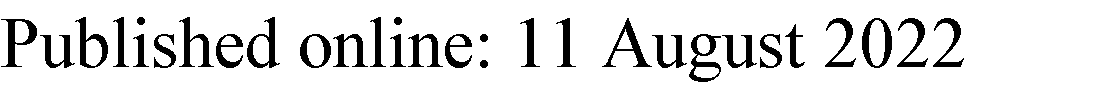
**Competing interests**

Shulamit Gellerstein and Nava Ben David were employees of Janssen Israel at the time of the study. The other authors declare no competing interests.

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