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Treatment resistant depression incidence estimates from studies of health insurance databases depend strongly on the details of the operating definition

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Abstract

Background: Health services databases provide population-based data that have been used to describe the epidemiology and costs of treatment resistant depression (TRD). This retrospective cohort study estimated TRD incidence and, via sensitivity analyses, assessed the variation of TRD incidence within the range of implementation choices.

Methods: In three US databases widely used for observational studies, we defined TRD as failure of two medications as evidenced by their replacement or supplementation by other medications, and set maximum durations (caps) for how long a medication regimen could remain in use and still be eligible to fail.

Results: TRD incidence estimates varied approximately 2-fold between the two databases (CCAE, Medicaid) that described socioeconomically different non-elderly populations; for a given cap varied 2-fold to 4-fold within each database

across the other implementation choices; and if the cap was also allowed to vary, varied 6-fold or 7-fold within each database.

Limitations: The main limitations were typical of studies from health services databases and included the lack of complete -rather than recent - medical histories, the limited amount of clinical information, and the assumption that medication dispensed was consumed as directed.

Conclusion: In retrospective cohort studies from health services databases, TRD incidence estimates vary widely depending on the implementation choices. Unless a firm basis for narrowing the range of these choices can be found, or a different analytic approach not dependent on such choices is adopted, TRD incidence and prevalence estimates from such databases will be difficult to compare or interpret.

Keywords: Evidence-based medicine, Psychiatry, Epidemiology, Health sciences, Clinical psychology

1. Introduction

Recurrent major depressive disorder (MDD) is a chronic disabling condition associated with high morbidity and appreciable mortality whose 12-month prevalence is estimated as 8% in the US and 3% to 6% in Europe [1, 2]. Its treatment often includes antidepressant (AD) medications and a substantial proportion of pharmaceutically treated depression (PTD) does not respond adequately to treatment with two or more antidepressant (AD) medications despite adequate dose, duration, and adherence to the antidepressant medications [3, 4, 5, 6]. Such cases are considered to have treatment resistant depression (TRD) [4] and carry higher personal and societal costs than do treatment-responsive MDD [7, 8]. Retrospective studies from health services databases, have often been used to describe the epidemiology and costs of TRD, but among such studies the proportion of PTD cases that develop into TRD cases ranges from 35% in a study limited to PTD subjects with a diagnosis of MDD [9] to less than 10% in a study that included a wider range of depression diagnoses among the PTD subjects [10].

The wide range of these estimates may reflect not only differences between populations and databases, but also differences in the definition of TRD and in how the definition of TRD is implemented to develop an estimate from the database. Making such implementation choices is required, and complicated, by the fact that the clinical information available in health services databases is quite limited and does not include direct measures of clinical status so the failure of a medication cannot be assessed from lack of clinical improvement. Thus, such studies often define the failure of a medication regimen by the introduction of a new medication. Among the required implementation choices are:

- Whether to include just AD medications or also other medications such as anti-psychotics (AP) as new medications whose introduction indicates the failure of an earlier regimen.

- Whether to place an upper limit (cap) on the time for a medication to be deemed to have failed because ineffective regimens are likely to be changed [11] and, if a cap is used, how long a time should be adopted as the cap.

- How many days' supply of a medication need to be dispensed before that medication can be considered to have been tried and failed. AD medications are believed to reach their full effectiveness only after approximately 6 weeks, but if no benefit is seen by 4 weeks, psychiatrists and patients may decide to make a change. Past studies have used minimum durations of 30 days or 42 days and the latter suggests enough compliance for the patient to have obtained a second dispensing [8, 11, 12].

- Whether to require that each AD medication be dispensed at or above a specified minimum dose in order to be considered to have failed and, if so, whether to waive that requirement if two AD medications are being used simultaneously.

- Whether to require a diagnosis of MDD, or to include a wider range of depression diagnoses because diagnostic coding in insurance claims databases is subject to up-coding (choosing a diagnosis that implies greater severity, e.g., to justify to the payer the use of more intense treatment) and down-coding (choosing a less severe diagnosis, e.g., to avoid stigmatizing the patient in future job applications).

We applied each of three baseline definitions of TRD, that were identical except for the cap on the maximum time for a regimen to fail, to each of three large US health services databases to describe the epidemiology of TRD, and used sensitivity analyses that varied selected characteristics of those definitions to explore the extent to which the estimated number of TRD cases varied within the range of credible choices for those characteristics.

2. Materials and methods

2.1. Study cohort

Data for this study came from three US health services databases from 1, Jan., 2010 through 31, Dec. 2014: Truven MarketScan Commercial Claims and Encounters (CCAE), with approximately 35 million mainly privately insured subscribers in 2011; Truven MarketScan Medicaid (MDCD), a means-tested public insurance program with approximately 5 million subscribers in 2011, and Truven MarketScan Medicare Supplemental Beneficiaries (MCDR), a public insurance program that is not means-tested, with approximately 3 million subscribers in 2011, most of whom were aged 65 or older. Each database is widely used for research. All analyses

were done in the Observational Medical Outcome Partnership (OMOP) Common Data Model (CDM) [13, 14], a standardized data structure with standardized vocabularies. This uniform formatting allowed us to generate the tables for each database from identical programs so differences across databases did not reflect differences in the analytic methods used. The CDM accommodates both ICD-9 and ICD-10. We described diagnoses by ICD-9 codes in this report because these were in use for most of the study period. Subjects entered the study cohort on 1 Jan, 2011 if they had been in the database for the past year (ignoring breaks of <30 days), had not had an exclusion diagnosis or a dispensing of an AD medication during that time, and were aged 14−60 years (CCAE or MDCD) or ≥65 years (MDCR). The cut at 60 was intended to avoid loss to follow-up from transfer to Medicare at age 65. Subjects left the study cohort with the first of: Leaving the database (ignoring breaks of <30 days), receiving an exclusion diagnosis, or reaching the end of the study (31December, 2014). The exclusion diagnoses were: Schizophrenia (ICD-9 code 295), bipolar disorder (ICD-9 codes 296.0, 296.1, 296.4−296.8), and dementia (ICD-9 codes 290, 294). MDD with psychotic behavior (ICD-9 code 296.24, 296.34) was not an exclusion diagnosis.

2.2. PTD definition

An episode of PTD began when a member of the study cohort received a dispensing of an AD medication and a diagnosis of depression between 180 days before and 30 days after that dispensing. The date of that dispensing was the episode's index date and had to be in 2011. A member of the cohort became a PTD case on the date of their first PTD episode and that date was the subject's PTD index date. As in Kubitz (2013) [10] and Fife (2017) [11], the episode of PTD ended with the first of: 1) No AD medication dispensings for 120 days (in which case the episode's duration was the number of days from the index date to the end of the days' supply of the last AD medication dispensed), or 2) leaving the study cohort (in which case the episode's duration was the number of days from the index date to the date of leaving the cohort). A subject could have more than one episode of PTD but each episode was required to begin in 2011.

2.3. Drug era, regimen

A drug era was defined as a sequence of dispensings of a single medication (an active drug substance, either an AD or AP) with each dispensing occurring within 30 days of the end of the days' supply of the previous dispensing. The era ended at the end of the days' supply of the last dispensing, with no 30 day "grace period" added. A regimen was any sequence of AD medications and (optionally) AP medications dispensings for which each medication's era is at least 28 days long. It began with the start or end of a drug era of one or more of its medications, i.e. with a change in the list of the subject's current AD and AP medications. It ended with the first of 1) A

new regimen (a regimen with a different list of current medications) began, or 2) The subject left the cohort. The list of current medications changed when a new AD or AP medication (a new drug substance) was dispensed, or when the drug era of one of the regimen's medications ended.

2.4. Failure of a regimen, failure of a medication, TRD

We used three definitions of failure of a regimen. The first 2 reflected the idea that a regimen would be changed if it failed to give adequate improvement within 90 days (90 days cap) or within 180 days (180 days cap), respectively. The third reflected the idea that a regimen failed if it didn't remain effective for a very long time (24 months cap). For the 90 days' cap, a regimen, regimen A, failed if at least 28 days after it began, but ≤90 days after it began, a new regimen, regimen B, was begun during the same PTD episode and regimen B contained an AD or AP medication that was not in regimen A and for at least one dispensing of each AD medication in regimen A the daily dose one week after its dispensing was ≥ the minimum effective dose. The one week offset is intended to avoid summing doses when a prescription is refilled a few days early. Regimen A failed when regimen B began. Regimen B did not need to begin immediately after regimen A ended. This is the definition of failure with a 90 day (3 month) cap. Failure with a 180 day (6 month) cap or a 730 day (24 month) cap is defined exactly the same except that 3 months is replaced by 6 months or 24 months.

2.5. Analysis

When a regimen fails, all the AD and AP medications in that regimen fail. A subject with PTD is considered to have TRD on the date when the second of his/her medications failed. A subject with PTD who did not meet the criteria for TRD and left the cohort during an episode of PTD (due to, e.g., meeting an exclusion criterion or reaching the end of the study) was classified as having unknown TRD status. For each database and cap, we tabulated the population at risk, incidence of PTD, and incidence of TRD, by sex and age group (data not shown) and, without stratification on sex or age group, estimated the prevalence of PTD as TRD incidence times duration. We also examined the AD and AP medications used to treat PTD and TRD. To assess the impact of the choices (parameters) selected to implement the definition of TRD on the estimated incidence of TRD, we calculated ratios of the maximum to minimum case counts with confidence intervals or p-values as appropriate.

3. Results

3.1. Subject selection

Table 1 shows the subject selection process. In each database, the most common unmet requirement was that of being in the database for at least a year prior to the start

Table 1. Subject selection.

Database	Private (CCAE)		Medicaid (MDCD)		Medicare (MDCR)	
	Retained	**Excluded**	**Retained**	**Excluded**	**Retained**	**Excluded**
Met age requirement[1]	25,791,353		1,905,877		3,042,893	
Not in database for ≥1 year		9,529,651		577,802		815,715
Exclusion diagnosis in past year		198,072		146,951		161,739
Dispensed an AD in past year		1,942,436		175,260		321,987
Study cohort[2]	14,121,194		1,005,864		1,742,452	
No AD dispensed in 2011		13,572,434		957,464		1,664,954
AD dispensed in 2011 but no accompanying depression diagnosis[3]		378,271		27,586		64,097
Incident PTD cases	170,489		20,814		13401	

[1] Age in 2011 was 14−60 years (inclusive) for CCAE and MDCD, or at least 65 years for MDCR.

[2] The population from which the pharmaceutically treated depression patients were identified, i.e., the base population from which incidence rates were calculated.

[3] To be considered an accompanying depression diagnosis, the diagnosis needed to be between 30 day before and 180 days after the AD dispensing.

2011. The most common reasons for a member of the cohort not to be an incident PTD case were lack of an AD medication dispensing during 2011 and, among those who were dispensed an AD medication in 2011, not having a depression diagnosis within the required time frame (180 days prior to or 30 days after the dispensing).

3.2. PTD and TRD incidence and prevalence

Table 2 shows by database the incidence, duration, and prevalence of PTD; and, by cap on the maximum time for a regimen to fail (3, 6, or 24 months), the incidence, duration, and prevalence of TRD. These estimates are quite precise, e.g., for the incidence estimate based on the smallest number of cases (TRD, 3 months' cap, MDCR), the half-width of the 95% confidence interval is 13% of the point estimate. In the two databases that included subjects aged ≤60 years (CCAE and MDCD), and with each cap, the incidence and duration of TRD were similar for subjects aged 14−17 years and for subjects aged 18−29 years (data not shown).

3.3. Medications

SSRIs was the class of AD medications most commonly used to treat PTD subjects. They were used in approximately 70% of first regimens and, though they appeared in a smaller percentage of second and third regimens, they remained the most common class of AD medications for the second and third regimens in all databases, both for subjects who developed TRD and for those who did not. In each database, and for each cap (3, 6, or 24 months), and for first regimens as well as second regimens, the

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Table 2. Incidence, duration, and prevalence of PTD and TRD stratified by database and cap on time to failure.

Database	Cap	Depression Type	N in cohort	Number of cases	Incidence estimate	Incidence 95% CI	Mean duration (years)	Prevalence estimate
CCAE	N/A	PTD	14,121,194	170,489	1207.32	1201.62, 1213.01	0.74	893.42
MDCD	N/A	PTD	1,005,864	20,814	2069.27	2041.45, 2097.09	0.56	1158.79
MDCR	N/A	PTD	1,742,452	13,401	769.09	756.12, 782.06	0.67	515.29
CCAE	3 months	TRD	14,121,194	4,791	33.93	32.97, 34.89	1.54	52.25
MDCD	3 months	TRD	1,005,864	661	65.71	60.71, 70.72	1.55	101.86
MDCR	3 months	TRD	1,742,452	228	13.08	11.39, 14.78	1.61	21.07
CCAE	6 months	TRD	14,121,194	7,130	50.49	49.33, 51.65	1.58	79.78
MDCD	6 months	TRD	1,005,864	987	98.12	92.01, 104.24	1.57	154.06
MDCR	6 months	TRD	1,742,452	320	18.36	16.36, 20.37	1.60	29.38
CCAE	24 months	TRD	14,121,194	9,038	64.00	62.69, 65.32	1.71	109.44
MDCD	24 months	TRD	1,005,864	1,209	120.20	113.43, 126.96	1.68	201.93
MDCR	24 months	TRD	1,742,452	404	23.19	20.93, 25.45	1.73	40.11

1 Incidence/100,000 cohort members/year.
2 Prevalence/100,000 cohort members.

percentage of subjects who were dispensed an AP medication was higher among TRD subjects than among PTD subjects who did not develop TRD. The ratios ranged from 1.5 to 3.7, and all were statistically significant $p < 0.01$ (Table 3).

3.4. Sensitivity analyses

Table 4 shows the number of TRD cases stratified by database and cap on maximum time for a regimen to fail (3, 6, or 24 months) for the main analysis as described in the Methods section, and for several variants on that analysis, e.g., changing the minimum days' supply of medication and minimum duration of a regimen to 42 days, or dropping the requirement for each AD medication to be dispensed at an adequate dose if the regimen contains more than one AD medication. Within the range of such choices about how to adapt the definition of TRD to a retrospective analysis of a health services database, the estimated number of TRD cases within each cap and database varied from 2.18-fold to 4.21-fold. If variation across the two shorter caps on the maximum time for a regimen to fail (3 or 6 months) is permitted, they varied 4.86-fold to 6.11-fold, and across all three caps they varied 6.27-fold to 7.66-fold.

4. Discussion

Our sensitivity findings demonstrate that within each database, the estimated incidence of TRD is sensitive to the key implementation choices used to define it, resulting in as much as a nearly 8-fold difference in TRD rates. This calls into question the utility of retrospective cohort studies of health services databases as a means of estimating the incidence and prevalence of TRD, or the proportion of incident PTD that becomes TRD, unless we can find well-substantiated reasons to narrow the range of definition choices, or can find a different approach to estimating TRD incidence and prevalence from health services databases.

We believed that the classification of a depressed patients as having MDD in the health services databases was unlikely to be the same as the classification used in clinical trials because the formal methods are more likely to be used in the latter, and because up-coding and down-coding are more likely to be present in the former [15, 16, 17, 18]. We therefore included a wider range of depression diagnoses but did not explore the effect of that decision. Only approximately 1/3 of the subjects in this study had an MDD diagnosis when they developed PTD, so adding that decision would have substantially expanded the already wide range of estimates in the sensitivity analyses.

4.1. Features seen across databases and caps

Notwithstanding the above, some features of PTD and TRD incidence and prevalence that were similar across definitions are worth noting. Because durations of TRD episodes were substantially longer than durations of PTD episodes, if

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Table 3. Proportions of first and second medication regimen that include an AP medication by database, TRD status (TRD vs. PTD that is not TRD), regimen (First or second) and cap on time to failure (3, 6, or 24 months).[1]

Database	Cap (months)	Regimen #1				Ratio of % with AP (TRD vs not TRD)	Regimen #2				Ratio of % with AP (TRD vs not TRD)
		Subjects with PTD but not TRD		Subjects with TRD			Subjects with PTD but not TRD		Subjects with TRD		
		N	% with AP	N	% with AP		N	% with AP	N	% with AP	
CCAE	3	123,439	2.75	4,791	7.58	2.8	41,791	3.38	4,791	8.98	2.7
CCAE	6	122,100	2.73	7,130	7.07	2.6	40,452	3.32	7,130	8.25	2.5
CCAE	24	121,206	2.70	9,038	6.94	2.6	39,558	3.29	9,038	8.00	2.4
MDCD	3	15,746	7.04	661	11.20	1.6	5,615	8.51	661	13.62	1.6
MDCD	6	15,522	7.00	987	10.64	1.5	5,391	8.31	987	13.98	1.7
MDCD	24	15,395	6.97	1,209	10.75	1.5	5,264	8.23	1,209	13.73	1.7
MDCR	3	8,365	2.83	228	8.77	3.1	2,021	3.71	228	8.77	2.4
MDCR	6	8,318	2.79	320	8.44	3.0	1,974	3.70	320	7.81	2.1
MDCR	24	8,295	2.78	404	10.15	3.7	1,951	3.69	404	9.65	2.6

For each database, cap, and regimen, each difference between the percentage who received AP medications among the subjects with TRD and the percentage among those with PTD but not TRD differed significantly p < 0.001 except for the second regimen in MDCR, where each cell met a criterion of p < 0.01.

[1] Table excludes subjects whose TRD status was unknown because they left the cohort during a PTD episode and had not met the criteria for TRD, and a small proportion of PTD subjects whose AD medication never met the 28 days' supply criterion for being a regimen.

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Table 4. Estimated number of TRD cases in the primary analysis and with several changes in the definition of TRD.

Database	Private (CCAE)			Medicaid (MDCD)			Medicare (MDCR)		
Cap (Maximum allowable time for a regimen to fail)	3 months	6 months	24 months	3 months	6 months	24 months	3 months	6 months	24 months
Main analysis	**4,791**	**7,130**	**9,038**	**661**	**987**	**1,209**	**228**	**320**	**404**
Min. days of use = 42 days AND Min days' supply = 42	1,364	2,807	4,299	191	395	588	74	140	213
AP meds not counted as failed	4,684	6,995	8,896	650	970	1,192	217	307	386
No Min. dose required in regimens with >1 AD Med.	5,741	8,340	10,451	769	1,146	1,389	252	360	464
Ratio of largest to smallest in the column	4.21	2.97	2.43	4.03	2.90	2.36	3.41	2.57	2.18
Ratio largest to smallest across 3 months and 6 months cap		6.11	N/A[1]		6.00	N/A		4.86	N/A
Ratio largest to smallest across 3, 6, and 24 months cap			7.66			7.27			6.27

[1] N/A = Not Applicable.

prevalence is estimated as incidence times duration the prevalence ratio of TRD to PTD is substantially higher than the incidence ratio of TRD to PTD. Practitioners deal mainly with prevalent cases so, relative to an incidence study, they may perceive TRD as a greater proportion of PTD.

The fact that the incidence and duration of TRD were similar for subjects aged 14–17 years and subjects aged 18–29 years suggests that it would be worthwhile to include younger age groups in future studies of the epidemiology of TRD.

Even in the first treatment regimen, AP medications were more often used among subjects who would subsequently develop TRD than among PTD subjects who would not develop TRD. Thus, a potentially important difference between PTD subjects who will develop TRD and TRD subjects who will not develop TRD is present before subjects can meet the criteria for TRD. However, it is worth noting that patients' lifetime history was not available in the database and this missing information may have been relevant to the choice of medications in what, for this study, was the first treatment regimen.

TRD clinical trials often retrospectively exclude subjects who develop an excluded diagnosis after entry. We did not use such retrospective exclusion because it is not considered good practice to do so in epidemiology studies, and we saw this more as a choice about the definition of TRD than a choice about how best to apply the definition of TRD to a retrospective cohort study. If subjects who developed an excluded diagnosis during the study period were retrospectively excluded from the cohort, the number of TRD subjects decreased approximately 10% in the CCAE database, 20% in the MDCD database, and more than 25% in the MDCR database regardless of the cap (3,6, or 9 months). This suggests that a substantial proportion of people who meet the criteria for TRD will develop an exclusion diagnosis within a few years afterward.

4.2. Limitations

Among the strengths of this study were the use of several large databases representing populations with different economic status and age ranges, and the use of standardized uniform data formats that let us apply identical analytic methods across those databases. Among the limitations were the lack of complete medical histories so cases had to be classified as incident based on recent rather than complete history; the limited amount of clinical information that made it impossible to distinguish between ongoing treatment for clinical depression and prophylactic treatment to prevent recurrence, and may have led to overestimation of the duration of depression episodes. We took as our baseline a widely used definition of TRD but there are others that are stricter or are more inclusive. Though it seems likely that similar issues would affect the application of these definitions to database studies, we have not

demonstrated that. Finally, we assumed that medication dispensed was consumed as directed.

4.3. Conclusion

In retrospective cohort studies from health services databases, TRD incidence estimates vary widely depending on several choices required to apply the definition of TRD. Unless a well-grounded basis for narrowing the range of these choices can be found, or a different analytic approach that does not depend on such choices [19] is adopted, estimates for the incidence and prevalence of TRD from such databases will be difficult to compare or interpret.

Declarations

Author contribution statement

Jenna Reps, M Soledad Cepeda, Paul Stang, Margaret Blacketer, Jaskaran Singh: Conceived and designed the analysis; Analyzed and interpreted the data

Daniel Fife: Conceived and designed the analysis; Analyzed and interpreted the data, Wrote the paper.

Competing interest statement

The authors declare the following conflict of interests: All authors are employees of Janssen Research & Development, LLC. Some authorshold stock, stock options, or pension rights in Janssen's parent company, Johnson & Johnson. Janssen, LLC Research and Development markets antipsychotic medications and is developing a medication fortreatment resistant depression.

Additional information

Data associated with this study were made available to the authors by third-party license from Truven MarketScan, a commercial data provider in the US, The authors have a license for analysis of the Truven MarketScan CCAE, MDCD, and MDCR data. Under the licensing agreement, the authors cannot provide the raw data themselves. Other researchers could access the data by purchase through Truven Market-Scan; and the inclusion criteria specified in the Methods section would allow them to identify the same cohort of patients we used for these analyses. Interested individuals

may see http://truvenhealth.com/markets/life-sciences/products/data-tools/market scan-databases for more information on accessing Truven MarketScan data. We confirm that no authors had special privileges to access data from Truven MarketScan via third-party license, and that other researchers would be able to access the data in the same manner as the authors.

Acknowledgements

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