PMH35

A Modelling Approach to Estimate the Prevalence of Treatment-Resistant Schizophrenia in The United States

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INTRODUCTION

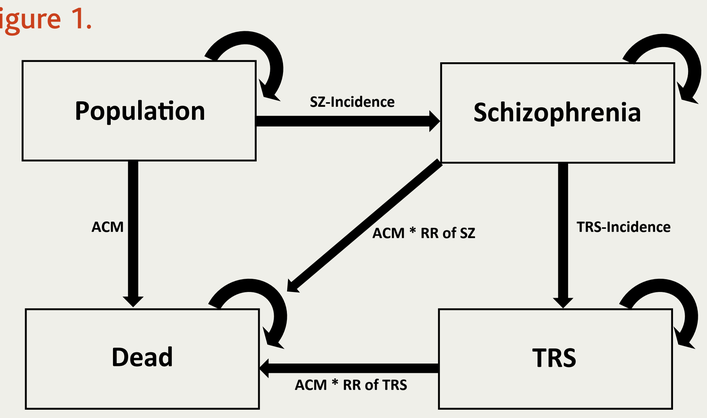
- Schizophrenia is one of the leading causes of disability within mental illnesses worldwide, and the debilitating disease results in a large impact on individuals and society (1). Individuals with schizophrenia have lower life expectancy, and reduced quality of life (2, 3). Furthermore, their relatives and caregivers also report significant impacts on daily activities (2).
- Some patients diagnosed with schizophrenia do only experience minimal to no symptomatic response from antipsychotic treatment and have so called treatment-resistant schizophrenia (TRS) (4-8). The only approved pharmacotherapy for TRS is clozapine, but its use is restricted by serious adverse events and the required monitoring for patients undergoing clozapine treatment (4, 9, 10). Additionally, half of the patients with TRS is intolerant or resistant to clozapine (11).
- The definition of treatment resistance is reported inconsistently across studies, and there is currently no ICD code for TRS, nor does DSM-5 include a diagnostic code (12, 13). Treatment-resistant schizophrenia is clinically defined as a condition whereby a person with schizophrenia symptomatology has no or minimal clinical improvement following ≥2 dopamine D2-preferring antipsychotics of adequate dose and duration, as assessed by a practicing clinician (4, 14, 15).
- It is described that up to 30% of all people with schizophrenia will at some point experience treatment resistance, although numbers vary significantly in the literature, where rates of 10-60% have been reported (4, 7, 16-18). In a Danish setting, using three different definitions of TRS, Wimberley et al (2016) reported a prevalence of 11%, 13% and 44% of patients with schizophrenia to be considered as having TRS (19), whereas 17% was reported in another study by the same author (20). In UK, Demjaha et al (2017) reported that among a small cohort of people suffering from first episode schizophrenia, 23% were reported as treatment-resistant (21).
- This discrepancy, both in the definition and prevalence of TRS in the literature makes it difficult to estimate the true burden of TRS, which has important implications for decision makers in health policy and providers. An important reason for the lack of consistency in prevalence estimates is the difficulty and expense of conducting large scale epidemiological studies in this subgroup of patients with schizophrenia. One way to address this is to construct a mathematical model to simulate the temporal changes in the population of patients at risk of TRS using validated epidemiological data. The aim of the present study was to estimate the prevalence of TRS in the United Stated using a modelling approach.

METHODS

- An Incidence-Prevalence-Mortality (IPM) model was used to estimate the prevalence of TRS in the United States. An IPM-model allows the investigator to estimate incidence, prevalence or mortality once two of the terms are known (22, 23). A Markov Model assumes that an individual is always in one of several specified health states, with probabilities of transitions between the states during each cycle (24). A one-year cycle was used for the following states in the study; Population, Schizophrenia, TRS and Dead. The population state are individuals in the cohort alive without a schizophrenia or TRS condition.
- Baseline incidence rates of schizophrenia were taken from a systematic literature review by McGrath et al (2008) (25). The incidence of TRS among patients with schizophrenia was taken from Wimberley et al 2016 (19). They estimated the TRS incidence rate with three different proxy definitions:

  1. Clozapine initiation
  2. Clozapine initiation or eligible for clozapine (main definition)
  3. Clozapine initiation, eligible for clozapine or 90 days' polypharmacy.

Figure 1.



*ACM: All-cause mortality. RR: Relative Risk. SZ: Schizophrenia. TRS: Treatment-Resistant Schizophrenia

- This study uses the second definition as the main definition to proxy TRS. To obtain age and sex adjusted incidence rates for TRS, the incidence was weighted to the distribution of US patients with similar proxy in the Truven Health Market Scan database for Medicaid patients (26). The incidence rates for schizophrenia and TRS were defined as annual risk to fit the one-year cycle in the model (27).
- The mortality risk of individuals with schizophrenia were based upon those found by McGrath et al and operationalized as standardized mortality rates (SMR) (25). A recent review found continuous clozapine use to be associated with 44% lower mortality rates compared to patients continuously exposed to another antipsychotics (28). The SMRs for TRS mortality was therefore adjusted proportionally adjusted when proxy 1 was used. The mortality risk was assumed to be similar between schizophrenia and TRS patients when proxy 2 and 3 was used. National statistics life tables provided by the U.S Social Security Administration was used as input to the age, gender and cohort specific mortality risks (29). US Population data for 2014 was applied from U.S. Census Bureau (31).
- The analysis were performed using the median incidence rate of schizophrenia and the median SMRs among schizophrenia patients reported in McGrath et al (2008) (25). Furthermore, a one-way sensitivity analysis was performed for the schizophrenia incidence input and the SMR rate inputs, where the reported 10th and 90th percentile of respectively incidence and SMRs was used. In addition, the model assumed no remission from the state of TRS to Schizophrenia, and no remission between the Schizophrenia state and population state.
- Applying the Markov Model assumptions with the incidence and mortality risks for each birth cohort between 1930-2014, the individual birth cohort was then modeled to 2014 for each of the four states: Population, Schizophrenia, TRS and Dead. Prevalence of TRS was calculated as the cross-section of all cohorts in 2014, as being in the TRS state and converted to prevalence per 10.000 in the US population.

RESULTS

- The prevalence estimates of the different TRS definitions, along with selected incidence rate of schizophrenia and SMRs are presented in Table 1. For each TRS definition, when the input parameters were changed, the estimated prevalence of TRS did, as expected, increase or decrease depending on scenario.
- The second proxy, which was the main scenario, together with the median incidence rate and SMRs, resulted in an estimated prevalence of TRS of 6.5 per 10.000 and a proportion of TRS of 21.5% among the schizophrenia population in the US in 2014. Comparing the one-way sensitivity analysis when changing the SMR rates while keeping the incidence rates constant, the model estimated an approximately 40% higher prevalence of TRS when using the 10th percentile of the SMR rate as compared to the 90th percentile. Likewise, for the one-way sensitivity analysis of incidence rate of schizophrenia, the estimated prevalence almost increased fivefold when comparing the 10th percentile of incidence rate to the 90th percentile. Regardless of parameter input, the proportion of TRS did not change within the three different proxies.
- The model found substantial impact on the estimated prevalence and the proportion of schizophrenia with TRS depending on proxy definition. The prevalence estimates were inflated almost five-fold between the first and third proxy. The proportion of TRS patients among patients with a schizophrenia condition differed between scenarios more than three-fold.

Table 1: TRS prevalence results estimated using the IPM-Model for USA 2014

Input Parameters			Proxy 1		Proxy 2		Proxy 3	
IR SZ[1] (M / F)	RR SZ[2] (M / F)	RR TRS[3] (M / F)	Prevalence per 10.000[4] (M / F / Total)	TRS proportion (%)[5] (M / F / Total)	Prevalence per 10.000 (M / F / Total)	TRS proportion (%) (M / F / Total)	Prevalence per 10.000 (M / F / Total)	TRS proportion (%) (M / F / Total)
Median Incidence & Relative Risk								
1.5 / 1.0	2.8 / 2.5	1.8 / 1.7	6.4 / 2.8 / 4.6	15.3 / 13.9 / 14.8	9.0 / 4.1 / 6.5	22.0 / 20.7 / 21.5	19.7 / 9.1 / 14.3	48.0 / 45.6 / 47.2
Incidence Rate Sensitivity								
0.7 / 0.3	2.8 / 2.5	1.8 / 1.7	3.0 / 0.8 / 1.9	15.3 / 13.9 / 15.0	4.2 / 1.2 / 2.7	22.0 / 20.6 / 21.6	9.2 / 2.7 / 5.9	48.0 / 45.6 / 47.4
3.4 / 3.0	2.8 / 2.5	1.8 / 1.7	14.5 / 8.4 / 11.4	15.3 / 13.9 / 14.8	20.4 / 12.3 / 16.3	22.0 / 20.7 / 21.5	44.5 / 27.2 / 35.8	48.1 / 45.7 / 47.1
Relative Risk Sensitivity								
1.5 / 1.0	1.7 / 1.5	1.1 / 1.0	7.4 / 3.1 / 5.2	15.7 / 14.1 / 15.2	10.6 / 4.6 / 7.6	23.0 / 21.3 / 22.5	23.1 / 10.2 / 16.6	49.9 / 46.8 / 48.9
1.5 / 1.0	4.7 / 5.4	3.1 / 3.6	5.2 / 2.2 / 3.7	14.5 / 13.3 / 14.1	7.2 / 3.2 / 5.2	20.5 / 19.2 / 20.1	16.0 / 7.1 / 11.5	45.5 / 43.0 / 44.7

Proxy 1 = Clozapine initiation. Proxy 2 = Clozapine initiation or eligible for clozapine. Proxy 3 = Clozapine initiation, eligible for clozapine or 90 days' polypharmacy
[1] Median Incidence Rate of schizophrenia per 10.000 for males and females. The 10th and 90th percentile incidence rate is used for sensitivity (15).
[2] Median Relative Risk of mortality in Schizophrenia state for males and females. The 10th and 90th percentile risk is used for sensitivity (15).
[3] Relative Risk of morality in TRS state for males and females (only used for Proxy 1). The TRS state in proxy 2 and 3 uses the same relative risk as the Schizophrenia state.
[4] Prevalence of Treatment-Resistant Schizophrenia per 10.000 for males, females and total.
[5] Proportion (%) of Treatment-Resistant Schizophrenia patients among people suffering from schizophrenia.

DISCUSSION

- An IPM-model was applied to model the prevalence and proportion of TRS patients among the schizophrenia population in the US. The one-way sensitivity analysis revealed the large impact on prevalence of changing incidence and mortality risks. The model estimated the proportion of TRS patients in the schizophrenia population to be in the range of 21-22% for the main scenario by applying incidence rates and SMR rates from McGrath et al (2008) (25).
- Despite the one-way sensitivity analyses revealed large variations in the prevalence estimates, all estimates for the different combination of proxies and parameter inputs are well within the range reported by Dammak et al 2013, who reported the proportion of TRS to be in the range of 5-60% (18). The large differences reported in Dammak et al 2013 can mainly be attributed different definitions of TRS. The results in this study suggests that the proportion of TRS patients is driven by the definition of TRS, whereas changing risk of mortality only shows minor impact. The prevalence of TRS per 10.000 was very sensitive to changes in the incidence rate of schizophrenia, which in the main definition of TRS, changed the prevalence from 2.7 to 16.3 per 10.000 when changing the incidence rate of schizophrenia from 0.7 to 3.4 per 10.000.
- The incidence rates used in this study were derived from a systematic review published in 2008 that summarized 158 studies of schizophrenia incidence (25). By applying the 10th and 90th percentiles of the incidence rates reported in literature, plausible ranges were derived under the different assumptions. A review and meta-analysis performed on UK studies reported a pooled incidence of schizophrenia of 15.2 per 100.000 person-years (30), which is almost identical to the median incidence rate reported in McGrath et al 2008 (25). Recently Castillejos et al (2018) reported a pooled incidence rate of 22.5 and 7.2 per 100.000 for non-affective and affective psychosis respectively (31). The plausible ranges well coincide with the estimated ranges by the model in this study.
- The applied SMRs in the model were derived from a systematic review containing 37 studies on mortality (25). A recent study from the US by Olfson el at (2015) (32), reported a relative risk of mortality of 3.7 from schizophrenia compared to the general population. The relative risk reported by Olfson et al (2015) is between the median and high SMR scenario in the one-way analyses, and the results in this study may thus be considered robust to changes in the SMR.

Figure 2: Prevalence per 10.000
Median incidence & Relative Risk

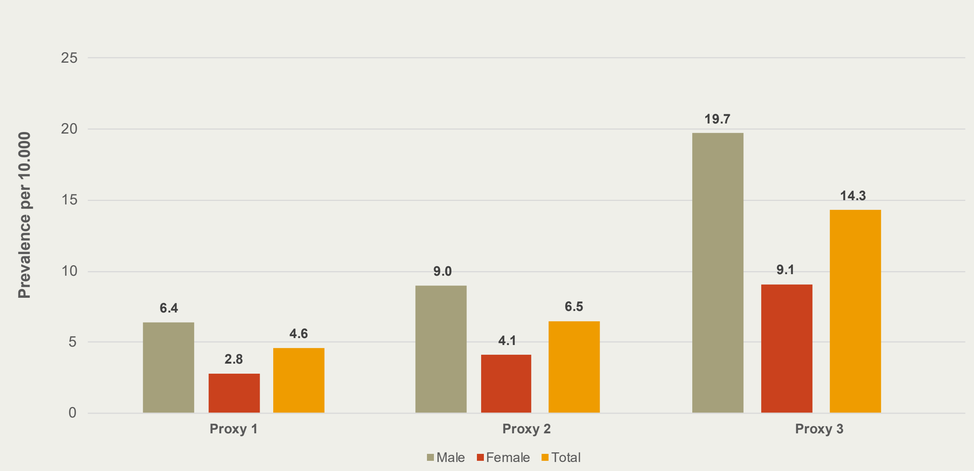
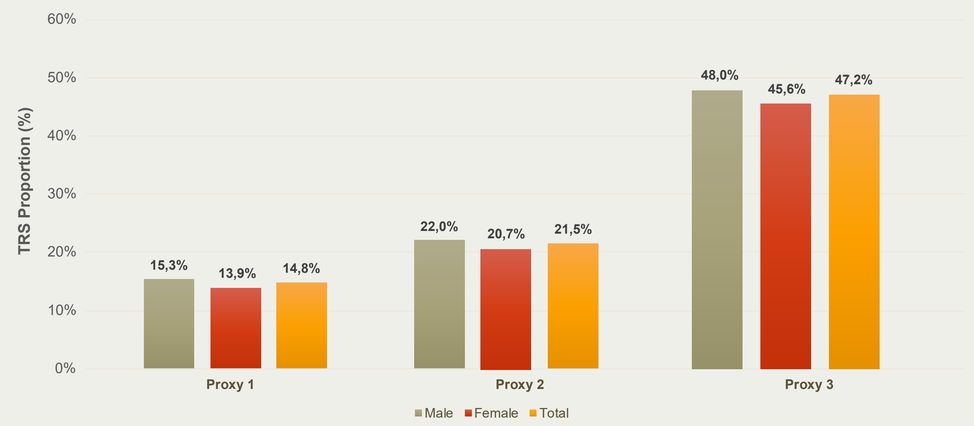


Figure 3: TRS Proportion (%)
Median incidence & Relative Risk



CONCLUSIONS

- The study estimated that approximately 22% of the schizophrenia patients had TRS in the United States for the main scenario.
- The estimates are highly dependent of proxy and as no uniform definition of TRS is available, estimating the true burden of TRS on individuals and society remains a challenging task.

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Funding:
This study was funded by Lundbeck

Conflict of Interest:
Michael Frank Mørup, Steven Kymes, Daniel Oudin Åström are employed by H. Lundbeck.

Poster presented at the ISPOR Annual European Congress, 2-6 November 2019, Copenhagen, Denmark.