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PROTOCOL

A Canadian Simulation Model for Major Depressive Disorder: Study Protocol

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Abstract

Background Major depressive disorder (MDD) is a common, often recurrent condition and a significant driver of healthcare costs. People with MDD often receive pharmacological therapy as the first-line treatment, but the majority of people require more than one medication trial to find one that relieves symptoms without causing intolerable side effects. There is an acute need for more effective interventions to improve patients' remission and quality of life and reduce the condition's economic burden on the healthcare system. Pharmacogenomic (PGx) testing could deliver these objectives, using genomic information to guide prescribing decisions. With an already complex and multifaceted care pathway for MDD, future evaluations of new treatment options require a flexible analytic infrastructure encompassing the entire care pathway. Individual-level simulation models are ideally suited for this purpose. We sought to develop an economic simulation model to assess the effectiveness and cost effectiveness of PGx testing for individuals with major depression. Additionally, the model serves as an analytic infrastructure, simulating the entire patient pathway for those with MDD.

Methods and Analysis Key stakeholders, including patient partners, clinical experts, researchers, and modelers, designed and developed a discrete-time microsimulation model of the clinical pathways of adults with MDD in British Columbia (BC), including all publicly-funded treatment options and multiple treatment steps. The Simulation Model of Major Depression (SiMMDep) was coded with a modular approach to enhance flexibility. The model was populated using multiple original data analyses conducted with BC administrative data, a systematic review, and an expert panel. The model accommodates newly diagnosed and prevalent adult patients with MDD in BC, with and without PGx-guided treatment. SiMMDep comprises over 1500 parameters in eight modules: entry cohort, demographics, disease progression, treatment, adverse events, hospitalization, costs and quality-adjusted life-years (payoff), and mortality. The model predicts health outcomes and estimates costs from a health system perspective. In addition, the model can incorporate interactive decision nodes to address different implementation strategies for PGx testing (or other interventions) along the clinical pathway. We conducted various forms of model validation (face, internal, and cross-validity) to ensure the correct functioning and expected results of SiMMDep.

Conclusion SiMMDep is Canada's first medication-specific, discrete-time microsimulation model for the treatment of MDD. With patient partner collaboration guiding its development, it incorporates realistic care journeys. SiMMDep synthesizes existing information and incorporates provincially-specific data to predict the benefits and costs associated with PGx testing. These predictions estimate the effectiveness, cost-effectiveness, resource utilization, and health gains of PGx testing compared with the current standard of care. However, the flexible analytic infrastructure can be adapted to support other policy questions and facilitate the rapid synthesis of new data for a broader search for efficiency improvements in the clinical field of depression.

Access to data provided by the Data Steward(s) is subject to approval, but can be requested for research projects through the Data Steward(s) or their designated service providers. All inferences, opinions, and conclusions drawn in this publication are those of the author(s) and do not reflect the opinions or policies of the Data Steward(s).

Extended author information available on the last page of the article

1 Background

Depression is projected to become the leading cause of disability by 2030 [1]. Major depressive disorder (MDD) is associated with higher rates of mortality [2], comorbidities [3], and a lower overall quality of life than the general population

Key Points for Decision Makers

Simulation Model of Major Depression (SiMMDep), the first Canadian whole disease model for major depression, assesses the effectiveness and cost-effectiveness of interventions by simulating sequential treatment decisions, considering past episode severity, and informing clinical decision-making and resource allocation.

SiMMDep accurately represents the major depression treatment pathways utilizing clinical trial results, administrative health sector data, as well as expert panel judgments, and incorporates input from patient partners to reflect real-world experiences.

SiMMDep incorporates 40 antidepressants, patient-specific attributes, and personalized decision-making, overcoming limitations of previous economic models.

[4]. While it has a lifetime prevalence of 11.2% in Canada [5], the global prevalence of depression has increased by 28% in 2020 due to the COVID-19 pandemic [6]. At an annual cost of $14 billion CAD, MDD presents a significant financial impact on patients and society [7]. There is, therefore, an urgent need for other interventions simultaneously to improve patients' quality of life and to reduce the economic burden of MDD on already strained healthcare systems.

Multiple effective treatments are available for depression, which commonly include pharmacotherapy and/or psychotherapy. However, >50% of people do not find their first antidepressant medication effective [8], and 30% still do not achieve symptom relief after several different medications [9]. This means that depression remains unsuccessfully treated for a sizeable proportion of those with MDD and for extended periods of time. More specifically, this can result in a painful and lengthy process of trial-and-error prescribing, which may lead to discontinuation with treatment, poorer long-term prognosis, and higher healthcare costs [10]. Interventions to reduce this trial-and-error period would, therefore, have far-reaching and significant benefits for those with MDD, their families, clinicians, and pharmacists, workforce productivity, and the health system.

Pharmacogenomic (PGx) testing, which involves generating prescribing recommendations based on genetic markers that indicate how quickly an individual metabolizes a medication, might confer such benefits. *CYP2D6* and *CYP2C19* genes are the main known contributors to antidepressant efficacy and side effects [11, 12]. Using PGx testing to guide prescription decisions could lower overall costs by matching patients with an efficacious medication and avoiding adverse effects in fewer overall drug trials. According to meta-analyses, using PGx testing can improve the rates of response and remission in the treatment of MDD [13–16]. However, cost-effectiveness evaluations are needed before decisions on implementing PGx as part of routine clinical care.

Simulation models are a powerful tool through which the long-term cost-effectiveness of new interventions can be explored. Although there are other health economics models of PGx testing for MDD, previous models included a narrow range of treatments for depression and only modeled outcomes for short time horizons [17–22]. These models may, therefore, lack some degree of external validity, underestimate treatment effects, and provide little indication of longer-term outcomes. A microsimulation modeling approach is ideal for examining MDD because treatment for depression (as well as the likelihood of its recurrence) is highly dependent on a patient's history with the condition (i.e., number and severity of past episodes) [23]. However, there are very few microsimulation models of MDD treatments.

In this paper, we describe a discrete-time microsimulation model, the Simulation Model of Major Depression (SiMMDep). This model-based analytic infrastructure was developed specifically to explore the effects of PGx testing on the prescription of antidepressants and subsequent outcomes in people with MDD in British Columbia (BC), Canada. SiMMDep meets a pressing need for a model that more closely matches MDD's chronic trajectory, considering multiple modes of treatment over the lifetime. The model encompasses the entire clinical pathway of MDD by simulating sequential treatment decisions, with a particular emphasis on pharmacotherapy treatment. It is a medication-specific model, which includes medications indicated for use in MDD treatment in the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines [24].

To our knowledge, this is the first whole disease model for MDD in the Canadian healthcare setting; namely, it simulates depression and treatment pathways from diagnosis to receiving treatment, discontinuing that treatment, full or partial remission, recurrence, development of refractory depression, and/or death. Taking a disease-level modeling approach assists with the reusability of the model for potentially any MDD intervention used at any point within the pathway, including pharmacotherapies, psychotherapies, and other more experimental treatments. This paper provides a detailed description of the components and data sources of the model, key outcomes, and the validation exercises undertaken. All findings from cost-effectiveness analyses using the model have been reported separately [25].

2 Methods

We designed and developed a discrete-time microsimulation model to simulate pathways followed by patients with MDD in BC, Canada. This was part of a larger project that aimed to examine the efficacy and value of PGx testing as part of routine care for patients with MDD compared with the current standard of care. As a result, this paper will describe the MDD model with specific consideration of model characteristics that are specific to the assessment of pharmacogenomics.

The team consisted of 25 key stakeholders, including patient partners [26], clinical experts, modelers, researchers, and policymakers. Consensus was reached through Zoom-based meeting discussions. It is the first Canadian microsimulation model for MDD care developed with guidance from patient partners. As described elsewhere in more detail, patient partners made major contributions to the design of SiMMDep, including verifying modeling assumptions, identifying model limitations, and offering insightful ideas for prospective future study fields [26].

SiMMDep is a discrete-time microsimulation model built in C++ with an interface in R, using the Rcpp package [27, 28]. It offers a flexible structure to model chronic conditions by reflecting the patient's history and its effect on the course of the condition over time [29, 30]. We followed guideline recommendations in the conceptualization of a decision-analytic model [31]. The model, with more than1500 input parameters, follows Canadian clinical guidelines for pharmacological treatments [24], incorporates estimates from a systematic review of randomized controlled trials [15], and adds local context by incorporating estimates from analysis of provincial administrative data [32–37] (e.g., prevalence, treatment, resource utilizations, costs). The cohort definition and the list of input parameters from BC administrative data are detailed in the electronic supplementary material (ESM, Appendix A).

SiMMDep was intentionally designed with a modular approach (eight interconnected modules) to enhance flexibility (Fig. 1) for future adaptations. Each module can be revised independently of the others and tailored for different contexts, interventions, or as new evidence emerges. We will first describe the function of each module, the source data, and the outcomes they generate. Then, we will describe the model validation process.

2.1 Entry Cohort Module

This module determines the target population represented in the model. First, it calculates the number of newly diagnosed and prevalent cases of MDD by multiplying the incidence and prevalence rates captured from BC administrative data [32–37] by the size of the adult (19+ years) population in BC. Further, it multiplies the number of newly diagnosed and prevalent patients by the ratio of patients on an antidepressant to estimate MDD patients eligible for pharmacological treatment when entering the model (ESM, Appendix A; Table A1).

2.2 Demographics Module

Upon entering the model, a unique set of attributes is assigned to each patient to resemble the specific characteristics observed within the actual cohort of individuals with MDD in BC. Some of these characteristics (e.g., metabolizer phenotypes, geographic ancestry) were derived in isolation from different sources, and so the estimated correlations with other parameters were not available. However, key demographic parameters (current age, sex, age at onset,

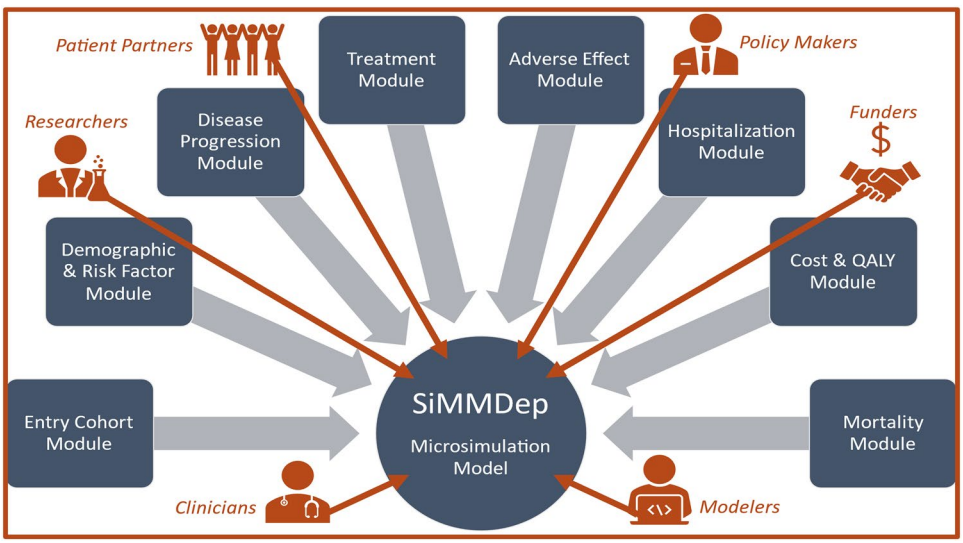

Fig. 1 Simulation Model of Major Depression (SiMMDep) modules (in rectangles) and contributors (represented with icons). This figure was reproduced from Ghanbarian et al. [25]

psychiatric comorbidity), as well as MDD history status (incident and prevalent), were estimated using BC administrative data [32–37] (see the ESM, Appendix A; Table A1 for more details). Hence, using a robust chain regression methodology, we established the correlation among variables as follows:

(a) The occurrence of MDD in the past (incident vs prevalent) was directly estimated from the available data as a binary variable;
(b) Sex was estimated separately within the incident and prevalent groups and represented as a binary variable;
(c) Current age was modeled using a truncated beta distribution, stratified by MDD history and sex;
(d) For prevalent patients, age at the onset of MDD was modeled as a linear function of current age within the respective strata of MDD history and sex;
(e) Psychiatric comorbidity was based on a logit model as a function of age, age at onset, and sex, within the strata of incident and prevalent groups.

For other characteristics, the model follows a multi-step approach. First, it assigns each patient a geographic ancestry category (European, East Asian, Central/South Asian, American, Near Eastern, Latino, Sub-Saharan African, Oceanian, African-American/Afro-Caribbean) due to variations in the frequency of actionable alleles among pharmacogenetic variants across ancestry groups [38–40]. The prevalence of each geographic ancestry group in BC was calculated using the 2016 Census results after matching to the PharmGKB categories above [41]. Next the model assigns each individual a metabolizer phenotype for the *CYP2D6* and *CYP2C19* genes, based on the prevalence of these metabolizer phenotypes in individuals with the same geographic ancestry, as sourced from PharmGKB [39, 40] and reported in Bousman et al. [42] (see the ESM, Appendix B for more details). Finally, the model assigns an MDD severity level (mild, moderate, or severe) to newly diagnosed and prevalent patients according to the MDD severity distribution from Ferrari et al. [43] and Kessing [44], respectively.

2.3 Disease Progression Module

Each patient's transition between three different health states (MDD, Well and Death) is captured over time in this module. The 'MDD' state includes three depression severity levels (mild, moderate, and severe), which are assigned to patients as they enter the MDD episode [43, 44]. The duration of each cycle is one week. The weekly cycle was chosen in order to give the model flexibility, especially to account for different potential outcomes along the clinical pathway. Event probabilities sourced from the literature [2, 23] and Statistics Canada [45] were converted to a 1-week time frame by transforming the probabilities to a rate (probability $= 1 - \exp(\text{-rate})$), adjusting the rate to the relevant time window, and then back-calculating the probability from the rate.

Patients can transition multiple times between different health states during their lifetime. Patients who move into the 'Well' state can remain well, recur to another episodic state, or die. Patients are followed until they reach 100 years of age, die (by suicide or other-cause mortality), or reach the end of the time horizon, whichever occurs first.

2.4 Treatment Module

This module encompasses the assessment of patient treatment at various time points (Fig. 2), including the process of selecting medications and monitoring the progress of patients along their respective pathways (Fig. 3). Five different MDD treatment pathways are included in this module (Fig. 3). The pathways were designed based on the CANMAT 2016 guidelines [24] and additional input from clinical experts and patient partners [26]. Each pathway includes various treatment options.

SiMMDep was developed from the perspective of public payers, and pharmacotherapy is usually the initial publicly-funded treatment option in BC. Psychotherapy coverage is typically offered only after multiple unsuccessful medication trials due to limited availability in BC, rather than according to CANMAT guidelines. Electroconvulsive therapy is the sole publicly-funded neurostimulation treatment. In SiMMDep, the MDD clinical pathway allows for up to five treatment trials of any of six increasingly intensive therapy choices for patients: (1) mono-pharmacotherapy (one antidepressant); (2) double pharmacotherapy (two antidepressants); (3) mono-pharmacotherapy plus psychotherapy; (4) double pharmacotherapy plus psychotherapy; (5) mono-pharmacotherapy plus electroconvulsive therapy (ECT); (6) double-pharmacotherapy plus ECT. If symptom remission is not achieved after five treatment trials in a single MDD episode, individuals are assumed to have *refractory depression*, also referred to in the clinical literature as Stage V treatment-resistant depression [46].

One advantage of the model is that it is drug-specific. It includes 26 main-line medications and 14 adjunctive medications, as recommended in CANMAT. The model only includes medications that are publicly covered to some extent by BC Pharmacare (ESM, Appendix A; Table A3).

2.4.1 Treatment Trial

Figure 2 presents the generic decision tree for any pharmacological treatment within an episodic MDD state. Upon entering the model, each patient is assigned a treatment option along with the treatment discontinuation and

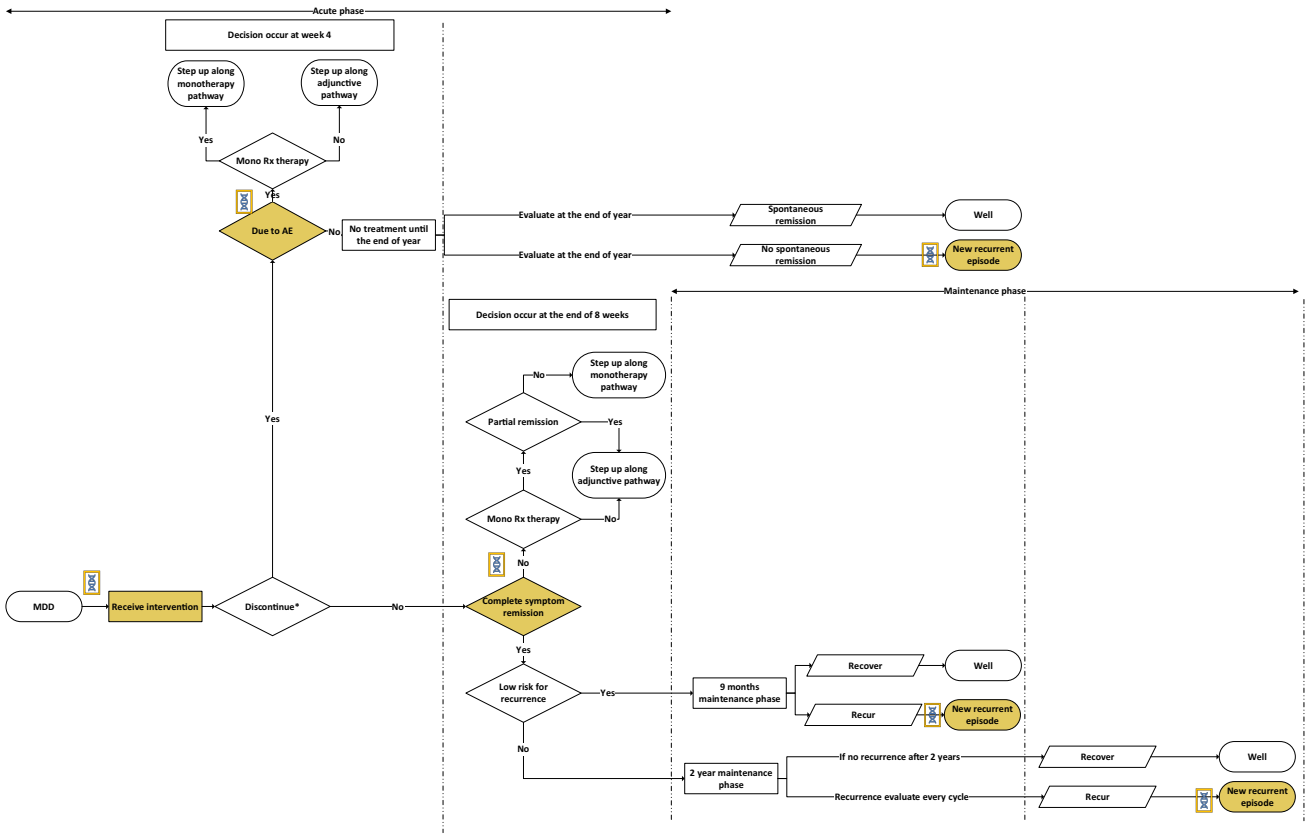

Fig. 2 The generic flow of patients with episodic MDD in a pharmacological treatment trial. *Dashed lines* separate the time points at which a pharmacotherapy treatment trial is evaluated for discontinuation, symptom remission/response, and depression recurrence (weeks 4, 12, 52, and 116, respectively). The PGx symbol represents the points along the pathway where the PGx testing can occur. Prevalent patients would receive the PGx testing prior to any prescription, and newly diagnosed patients would receive the PGx testing after one unsuccessful medication trial. In both instances, only patients with moderate to severe MDD would receive PGx testing. * Discontinuation may be due to adverse effects or other reasons (e.g., feeling better or experiencing other serious diseases). *MDD* major depression disorder, *AE* adverse effect (e.g., nausea, weight gain), *PGx* pharmacogenomics. This figure was reproduced from Ghanbarian et al., 2023 [25].

remission probabilities associated with that treatment from published literature [47–50] (ESM, Appendix D). The model then follows patients through two phases of depression treatment: an acute phase (achieving clinical remission) and a maintenance phase (avoiding recurrence).

Four weeks after initiating the medication, the model assesses treatment discontinuation based on the probability distribution that was extracted from the published literature (ESM, Appendix D) [47, 48]. Those who discontinue the medication fall into two categories: (1) discontinuation due to adverse effects; (2) discontinuation for reasons other than adverse effects (for example, feeling better, dealing with another serious illness, etc.). Any patients who discontinue medication for reasons other than adverse effects are assumed to remain without treatment until the end of the year. Thereafter, they either move to the 'Well' state (due to spontaneous remission) or experience a recurrent episode, according to our clinical advisor. The estimated value for the probability of remission of untreated patients was calculated using the weighted mean average of the placebo arm of randomized clinical trials from an existing systematic review and network meta-analysis [47] (ESM, Appendix F).

If the patient continues their medication after 4 weeks, the model assumes they have an assessment at 12 weeks for symptom remission, which may be either full or partial, defined as follows:

- Full remission: Patients are assigned a *high* or *low* probability of recurrence, which determines the length of their maintenance phase (i.e., on medication). Based on CANMAT guidelines, 'high risk' is characterized as meeting any one of the following criteria: having other psychiatric comorbidities, experiencing a severe MDD episode, or enduring a current or previous depression episode last-

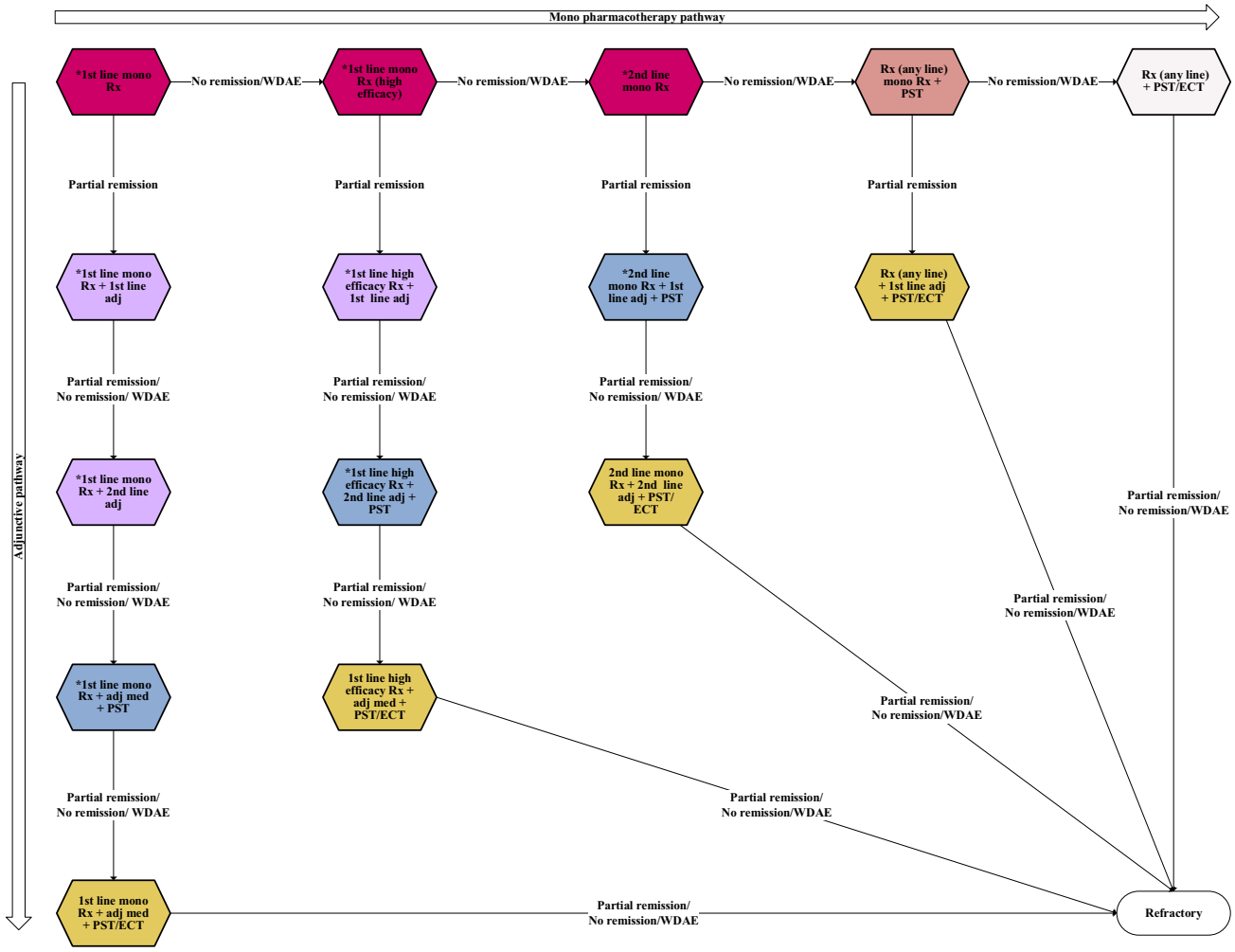

Fig. 3 Current clinical care pathway for patients with major depressive disorder in British Columbia, Canada. The clinical pathway includes six treatment options, represented by different colors in the graph. Newly diagnosed patients were assumed to start from the beginning of the pathway. The model assigns prevalent patients to one of the nine starting points, represented by asterisks, based on the prescription patterns from the BC administrative data [32–37]. *adj* Adjunctive, *ECT* electroconvulsive therapy, *med* medication, *mono* monotherapy, *PST* psychotherapy, *Rx* prescription pharmacotherapy, *WDAE* withdrawal due to adverse effects. This figure was reproduced and modified from Ghanbarian et al., 2023 [25]

ing over 2 years. These patients enter a 2-year maintenance phase, which includes 3 months of tapering off the medication (if applicable). After 2 years, the patient is either well or starts a new recurrent episode. To represent patients who remain on a long-term maintenance dose of medication (that is, after the maintenance phase), the model assumes that the majority of high-risk patients in the 'Well' state continue medication treatment, with a portion gradually tapering off their medication according to our clinical experts. Patients with a 'low risk' of recurrence (i.e., did not meet any of the above 'high risk' criteria) enter a 1-year maintenance phase, which includes 2 months of tapering off the medication. At the end of this year, the patient is either well (full remission) or begins a new MDD episode (recurrence). Risk of depression recurrence depends on age, age of onset, history of any episode, and history of severe episodes, according to the study by Hardeveld et al., 2013 [23]. Therefore, the model keeps a record of patients' previous episodes. The risk of recurrence is calculated based on a multifactorial equation that includes all patient-related risk modifiers, as mentioned above. We calculated the baseline probability of recurrence, excluding those with previous recurrent and severe episodes, to avoid double counting after applying the ratio modifier equation (ESM, Appendix F). Once the recurrent episode was determined, their MDD severity followed the distribution by Kessing for MDD recurrent episodes (ESM, Appendix C) [44].

- Partial remission: Patients that experience some, but not complete, symptom remission, step up along the adjunc-

tive therapy pathway. In this scenario, the model brings the patient back to the start of a new treatment trial and they subsequently progress through the treatment pathway.

SiMMDep offers PGx testing at different time points along the pathway, depending on the severity of the current episode and the patient's previous history of MDD for the base-case cost-effectiveness analysis. For patients with mild MDD, PGx testing is conducted if MDD recurs as a moderate or severe episode. However, for patients with moderate and severe MDD, testing is done before any prescription for prevalent patients and after one unsuccessful medication trial for newly diagnosed patients. This decision was guided by experts in the field and is in line with several US insurance policies and other economic analyses [21]. For the patients with PGx testing, the model modifies the likelihood of treatment discontinuation (due to side effects or other reasons) and remission (partial and full), according to our meta-analysis results [15].

2.4.2 Medication Selection

The model selects medication for each patient based on (1) CANMAT 2016 guidelines [24], (2) the patient's antidepressant history (recorded in the model), and (3) the patient's PGx test results (if available).

1. The CANMAT guidelines [24] recommend a list of antidepressants for adult patients with MDD sorted into first-line medications, first-line "superior efficacy" medications, second- and third-line medications. In actual clinical practice, however, selecting an antidepressant involves physician expertise and patient perceptions and preferences. We emulated this process in the model by assigning medications to hypothetical patients according to the actual distribution of antidepressant medications currently prescribed in BC (ESM, Appendix A, Table A3.2).
2. A patient's antidepressant history determines and limits the choice of antidepressant in the subsequent treatment trials. The model records each patient's medication history. When assigning a new medication, the model excludes medications that have previously caused an adverse event or which did not result in full symptom remission for the patient (i.e., are considered ineffective for that patient). Then, the model adjusts the medication distribution based on the antidepressants that can still be prescribed and selects one based on the distribution of antidepressant prescriptions in BC [32–37].
3. For those with PGx testing, the model operationalizes the medication recommendations based on an individual patient's CYP2D6 and CYP2C19 metabolizer phenotypes. We built a list of eligible medications available for each patient using the Clinical Pharmacogenomics Implementation Consortium (CPIC) guidelines [39, 40, 51–53] and the Sequence2Script tool [54]. To account for all possible combinations of CYP2D6 and CYP2C19 metabolizer phenotypes, the model removes all contraindicated medications for both metabolizer phenotypes in isolation, then creates a selection list of treatment options. Finally, the model assigns a medication from this remaining list, based on a normalized probability distribution, to account for any removed medications (ESM, Appendix E).

The model ensures there are no negative interactions between the primary and adjunctive medications, according to the Canadian Pharmacists Association's Lexicomp® Interactions Module [55] (ESM, Appendix G).

2.4.3 Clinical Pathway of Newly Diagnosed and Prevalent Patients

SiMMDep assumes that all newly diagnosed patients would start from the first treatment trial with a first-line mono-pharmacotherapy treatment (Fig. 3). However, to account for the patient's history of any previous antidepressant trials, the model assigns each prevalent patient to one of nine starting points along the mono-pharmacotherapy or adjunctive therapy pathways (marked by asterisks in Fig. 3). We calculated the probability of being assigned to any starting point using the prescription patterns from the BC administrative data (ESM, Appendix A3, Table A3.1). Patients can transition to the 'Well' state, 'Death' state, or continue treatment by moving along either the mono-pharmacotherapy pathway or adjunctive pathway.

In the monotherapy pathway (Fig. 3, horizontal line), the second treatment trial is a first-line treatment that CANMAT [24] rates as having "superior efficacy"; specifically, escitalopram, mirtazapine, sertraline, venlafaxine, and citalopram. The model assigns one of these medications (if not prescribed in the first trial) based on prescription patterns in BC (ESM, Appendix A3, Table A3.1). If any of these medications are unsuccessful at bringing about remission, patients move to the third mono-pharmacotherapy treatment trial, which uses a second-line antidepressant. In the fourth treatment trial, a third-line antidepressant is prescribed in combination with psychotherapy (stemming from the assumption that patients will qualify for publicly paid psychotherapy at this point). According to BC administrative data [32–37], the prescription of third-line antidepressants is relatively small. Therefore, the model assigns patients any antidepressant they have not previously tried or one that has not caused adverse effects. The fifth and final step of the mono-pharmacotherapy pathway is a different antidepressant

(not previously tried or that has not caused adverse effects) with the addition of either a new course of psychotherapy or ECT. If patients do not achieve full remission or discontinue treatment due to an adverse event at this stage, the model labels their depression as refractory.

If a patient experiences partial remission with a first-line mono-pharmacotherapy, they move to the adjunctive pathway and do not return to the mono-pharmacotherapy pathway. In the adjunctive pathway (Fig. 3, vertical line), the second treatment trial includes adding a first-line adjunctive medication to the original first-line pharmacotherapy. Adjunctive medications are assigned based on observed prescription patterns in BC from the administrative data (ESM, Appendix A3, Table A3.2). If the second treatment trial does not result in full remission, the model replaces the adjunctive medication with a second-line one. Should the patient require another replacement of the adjunctive medication, this will be in combination with psychotherapy in the fourth treatment trial. Finally, in the fifth treatment trial, patients receive new adjunctive medication and another course of psychotherapy or ECT. If patients do not experience complete remission or discontinue treatment due to an adverse event at this point, the model labels them as having refractory depression.

2.5 Adverse Effect Module

The module incorporates a two-step approach for treatment discontinuation, utilizing a probability distribution derived from the published literature (ESM, Appendix E) [47, 48]. As explained above, first, the probability of total discontinuation (for any reason) is assigned after 4 weeks of medication initiation. Then, for those who discontinue their treatment, the model applies the probability of discontinuation due to adverse effects. The CPIC antidepressant guidelines highlight that common side effects of antidepressants include gastrointestinal dysfunction, sexual dysfunction, and impacts on the central nervous system (such as insomnia) [56]. However, it is important to note that the incidence and type of side effects vary by antidepressant. Therefore, to capture the effect of PGx testing on adverse effects, the pooled probability of discontinuation from our systematic review was used [15].

2.6 Hospitalization Module

Patients with MDD have a higher risk of all-cause hospitalization than those without depression, reflecting the impact of depression on both mental and physical health [57]. This module assigns patients' weekly probability of all-cause hospitalization and counts the number of hospital admissions. Acute all-cause hospitalization can occur for patients at any point along the clinical pathway. We calculated hospitalization rates for people with MDD (episodic and refractory) from the BC administrative data [32–37]. For the patients in the 'Well' state, the model assigns the general Canadian population's all-cause hospitalization rate [58] (ESM, Appendix A4).

2.7 Cost and QALY Module

This module captures all treatment-related costs and benefits from the public payer's perspective. It assigns costs and health utility values to patients at different times along the clinical pathway according to their health states and the events (e.g., hospitalization, suicide) they experience. We adjusted all costs to 2023 Canadian dollars using the healthcare component of the Consumer Price Index [59], and discounted costs and benefits at 1.5% annually [31].

As patients go through different health states and events in the model, their costs and health service use are estimated. We used multiple sources for costing: the BC administrative databases for publicly-funded healthcare costs [32–37], Canadian Institute for Health Information (CIHI) [58], Medical Services Commission (MSC) payment schedule [60], Health Employers Association of BC [61], published literature [62], and our expert review panel (when data was unavailable). The model includes the cost of antidepressants covered by PharmaCare, psychotherapy (individual cognitive behavioral therapy [CBT]), ECT, hospitalization, monitoring and assessments with healthcare professionals, and PGx testing. The model does not simulate the details of the care pathway for patients after they develop refractory depression. Instead, it assigns the average weekly costs to the patients with refractory depression found in the BC administrative data [32–37] (see the ESM, Appendix H for full details of the costing exercise).

All patients enter the model with an MDD-specific utility value stratified by their health state, the severity of MDD, and remission status (ESM, Appendix I). The utility values we applied referenced a large dataset of EQ-5D-3L responses from over 1900 participants from 10 different depression trials [4], population norms for Canadians, and longitudinal studies for patients with refractory MDD [63]. All utility index values that we reference were scored according to the tariffs for the UK population in the absence of Canadian tariffs. Therefore, we assumed that Canadians' preferences for health are similar to those in the UK. We also assume that health-related quality of life improves for all patients upon remission of their MDD. Finally, we assumed the quality of life of MDD patients returned to that of the general population after recovery [64].

2.8 Mortality Module

This module tabulates death due to any cause, including causes specific to MDD. We assumed patients in the 'Well' state have the same mortality rate as the general population. We applied a weekly age- and sex-specific mortality rate based on the annual rate reported by Statistics Canada [45]. The model assumes that patients with episodic MDD and patients with refractory MDD have a higher mortality risk than the general population, and their relative risk was applied to the background mortality [2, 65] (ESM, Appendix J).

The background mortality and the respective relative risk estimated the risk of all-cause mortality, including death due to suicide. We estimated the number of deaths due to suicide by applying the specific probability of death due to suicide to the total number of deaths in each health state, after applying background mortality and disease-relative risks [66].

3 Model Validation

To ensure that SiMMDep was functioning correctly and producing results as expected, we followed the guidelines in establishing validation targets [67]. A group of clinical experts (including a family doctor, a psychiatrist, and a psychologist) and two patient partners closely checked all the assumptions behind the structure of the clinical pathway. In addition, they helped to define the parameters within the administrative data to populate the model. As a result, the research group ensured that SiMMDep produces sensible and expected results (ESM, Appendix K, Table K1.1).

A senior health economist performed validation by reviewing the equations and methods utilized. For internal validation, we aimed to ensure that the model's outputs matched patterns observed in input data sources or calibration targets. For example, the ratio of patients experiencing full/partial remission with and without PGx testing matched the ratio found in the meta-analysis [15]. The validation process encompassed various modules within the model, and a list of validations conducted is provided in Table K2.1 (ESM, Appendix K). Finally for cross-validation, we compared the cost-effectiveness outcome of PGx testing for MDD in SiMMDep and a recent Canadian health technology assessment (HTA) [21]. We ran the model using a shorter time horizon and aimed to align key assumptions such as population, PGx testing price, specific health utility values, and the scenario for delivering PGx. While achieving similar results in this cross-validation, we assert that our assumptions are well justified, and it is crucial to model long-term outcomes for this recurrent mental health condition.

4 Discussion

The current study introduces SiMMDep, the first whole disease model for MDD in Canada, which was developed in collaboration with patient partners, clinicians, and a multidisciplinary team of researchers. The model encompasses a range of publicly-funded treatments for major depression, and enables cost-effectiveness evaluations of PGx testing or other interventions to treat depression within the Canadian context. In this way, SiMMDep facilitates evidence-based policy decisions and potentially enhances access to mental health services by covering the entire clinical pathway of major depression.

This discrete-time microsimulation model was specifically designed to address major depression in Canada, with a particular emphasis on pharmacological treatment, but also included psychotherapy and ECT. The model integrates data from various sources, such as estimates from systematic reviews of randomized controlled trials [15], administrative health sector data [32–37] on 194,149 adults with MDD, input from a panel of clinical experts, and multiple published studies. The model incorporates 40 antidepressants indicated for MDD treatment, allowing for sequential treatment decisions in line with clinical guidelines. In addition, it considers various therapeutic options and incorporates patient attributes, including metabolizer phenotypes, geographic ancestry, and MDD history. SiMMDep was applied to assess the costs, resource utilization, and health gain of PGx testing compared with the current standard of care in BC over patients' lifetime. The outcomes of the cost-effectiveness analysis of interventions are reported separately [25].

Existing economic models for MDD often concentrate on particular treatments while neglecting the gradual escalation in treatment intensity advised by clinical guidelines [22]. Commonly, these models typically disregard individual patient attributes and do not encompass the enduring effects of interventions [17–21]. SiMMDep is a major advance in modeling MDD in Canada as it overcomes the limitations mentioned above and offers a comprehensive framework for assessing a wide variety of treatment scenarios.

Despite its strengths, SiMMDep has certain limitations. While it presently models assessments and recurrence at defined time intervals, the model's flexible framework allows for the future incorporation of customizable timelines for each individual patient. It is important to acknowledge that in the absence of available evidence, SiMMDep does not simulate the details of the clinical pathway for refractory depression. The model assumes average weekly expenditures of all comorbidities and treatments for such patients, average health quality, and mortality rates. SiMMDep does not encompass sub-threshold symptomatic patients or interventions that target prevention of the condition. The

primary goal of developing SiMMDep was assessing PGx testing and sub-threshold symptomatic patients are not often offered pharmacological treatment as their initial treatment and, therefore, were not the target population. Furthermore, we utilized health utility index values scored based on UK population tariffs, assuming similarity in health preferences between Canada and the UK due to the absence of Canadian tariffs. These limitations should be considered when interpreting the results and evaluating the applicability of SiMMDep in addressing other research questions.

5 Conclusion

SiMMDep was initially developed to estimate the benefits and costs of pharmacogenomic tools targeting people with major depression. However, the modular approach enhances its flexibility to evaluate diverse and/or future policy options across the treatment continuum, and it can be tailored to various jurisdictions. It is our hope and aim that SiMMDep can serve as an analytical infrastructure for evaluating various treatment options to improve the quality, efficiency, and equity of care delivery for depression in Canada.

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Declarations

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Conflict of interest Christian Schuetz reports research funding from the Provincial Health Service Authority, Health Canada, Canadian Institutes of Health Research, Canadian Centre on Substance Use and Addiction (CCSA) and Clairvoyant; consulting fees from CCSA; and travel support from Suchtmedizin. He is chair of the addiction and psychosis committee of the International Society of Addiction Medicine; research lead, Mental Health and Addiction to the Provincial Health Services Authority; division head, Substance Use, and Concurrent Disorders with the University of British Columbia; and sits on the scientific committee of the World Association on Dual Disorders. Moreover, he serves on the scientific board of Clearmind. Jehannine Austin is vice president of the International Society for Psychiatric Genetics and associate editor with the Journal of Genetic Counseling. No other competing interests were declared.

Ethics approval This project was approved by the University of British Columbia Clinical Research Ethics Board (#H20-02362).

Consent to participate Not applicable.

Consent for publication Not applicable.

Data availability The main input parameters can be found in the electronic supplementary material (Appendices A–J), where detailed information regarding the data used in the study is reported. However, the resources from which these parameters were derived have been cited as references throughout the document to ensure accuracy and reliability.

Code availability The code may be made available by the corresponding author, upon reasonable request.

Author contributions The authors of this study meet the authorship criteria outlined by the International Committee of Medical Journal Editors (ICMJE). JA and SB designed the original research question. SG developed, programmed, validated, and analyzed the discrete-time microsimulation model. GW and MB conducted a rapid literature review, sourced relevant literature, and performed meta-analyses to provide input parameters for the model. They also assisted with model validation checks. SC and TC contributed cost inputs for the model, while RV and SP, under the guidance of KM, prepared and analyzed administrative data for the model. MP, CS, and DE provided clinical expert opinions in cases where estimates from the literature were not available. GW, MB, MP, CS, DE, GL, LR, RV, LE, and SB reviewed and verified model assumptions. LR and GL ensured that the clinical pathway reflected real-world patient experiences. SG drafted the manuscript, which LE, SB, JA, and GW subsequently revised. All authors have thoroughly reviewed and approved the final manuscript for publication.

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