Supplementary Appendix 1 - The Medication Quantification Scale 4.0 (MQS-4.0)

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The Medication Quantification Scale 4.0 (MQS-4.0)
An updated index based on prescribers' perceptions of the risk associated with chronic pain medications

	MEDICATION SUBCLASSES	EXAMPLES OF MEDICATIONS*	RISK SCORES (DETRIMENT WEIGHTS)
1	Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) – Selective cyclooxygenase 2 inhibitors (COX-2)	celecoxib (Celebrex®)	5
2	NSAIDs – Salicylates	acetylsalicylic acid (ASA, Aspirin®)	5
3	Other oral NSAIDs	ibuprofen (Advil®, Motrin®), naproxen (Naprosyn®), diclofenac, ketoprofen, meloxicam, piroxicam	6
4	NSAIDs – Topical agents	diclofenac sodium (Pennsaid®), diclofenac diethylamine (Voltaren Emulgel®)	2
5	Various topical agents	various magistral preparations, ketamine cream, benzocaine, lidocaine (Emla®), capsaicin (Zostrix®), Antiphlogistine®, Myoflex®, Tiger Baulm®	2
6	Acetaminophen	Tylenol®	2
7	Acetaminophen in combination with an opioid	acetaminophen with codeine (Triatec-30®, Emprac-et®), with tramadol (Tramacet®) or with oxycodone (Percocet®)	6
8	Short-acting opioids	codeine, fentanyl, hydromorphone, morphine, oxycodone	8
9	Long-acting opioids	methadone, extended release formulations (Codeine Contin® OxyContin®, Hydromorph Contin®, Jurnista®, MS Contin®, Duragesic®)	8
10	Opioids associated with norepinephrine reuptake inhibition	tramadol, tapentadol	6
11	Partial opioid receptor agonists	buprenorphine (Butrans®), butorphanol	6
12	Opioids in combination with an opioid receptor antagonist	buprenorphine/naloxone (Suboxone®), oxycodone/naloxone (Targin®)	6
13	Anticonvulsants – Calcium channel blockers (gabapentinoids)	pregabalin (Lyrica®), gabapentin (Gabapentin®)	5
14	Anticonvulsants – Sodium channel blockers	oxycarbazepine, lamotrigine (Lamictal®)	6
15	Anticonvulsants – Other	levetiracetam (Keppra®), topiramate (Topamax®)	6
16	Antidepressants – Serotonin norepinephrine reuptake inhibitors (SNRIs)	duloxetine (Cymbalta®), venlafaxine (Effexor XR®)	4
17	Antidepressants – Selective serotonin reuptake inhibitors (SSRIs)	citalopram (Celexa®), escitalopram, fluvoxamine (Luvox®), fluoxetine (Prozac®), paroxetine (Paxil®), sertraline (Zoloft®)	4
18	Antidepressants – Serotonin reuptake inhibitors and 5-HT2 receptor antagonists	trazodone	4

	MEDICATION SUBCLASSES	EXAMPLES OF MEDICATIONS*	RISK SCORES (DETRIMENT WEIGHTS)
19	Antidepressants – Specific noradrenergic and serotonergic	mirtazapine (Remeron®)	4
20	Antidepressants – Tricyclic	amitriptyline (Elavil®), nortriptyline (Aventyl®), desipramine	5
21	Antidepressants – Miscellaneous	bupropion (Wellbutrin®)	4
22	Antipsychotics	aripiprazole, chlorpromazine, clozapine, haloperidol, olanzapine (Zyprexa®), quetiapine (Seroquel®)	6
23	Barbiturates	phenobarbital, primidone	8
24	Benzodiazepines	lobazam, clonazepam (Rivotril®), alprazolam (Xanax®), bromazepam, chlordiazepoxide, diazepam (Valium®), flurazepam, lorazepam (Ativan®), midazolam, oxazepam	8
25	Various anxiolytics, sedatives, and hypnotics	buspirone, hydroxyzine (Atarax®), promethazine, zopiclone, zolpidem tartrate	6
26	Centrally acting skeletal muscle relaxants	cyclobenzaprine (Flexeril®), methocarbamol (Robax®)	5
27	GABA-Derivative skeletal muscle relaxants	baclofen (Lioresal®)	5
28	Miscellaneous muscle relaxants	orphenadrine (Norflex®)	4
29	Synthetic cannabinoid (under prescription)	nabilone (Cesamet®)	6
30	Medical/therapeutic cannabis	vaporized, vaped, oral, oromucosal, topical	6
31	Antimigraine agents – 5HT-1 receptor agonists (triptans)	sumatriptan (Imitrex®)	4
32	Antimigraine agents – Calcitonin gene-related peptide (CGRP) antagonists	erenumab (Aimovig®)	4
33	Antimigraine agents – Miscellaneous	pizotifen (Sandomigran®)	5
34	Corticosteroids – Oral	prednisone, prednisolone	7

* According to medications approved and available in Canada at the time of the study.

STEPS FOR CALCULATING THE MQS-4.0 SCORE, A MEASURE OF THE RISK ASSOCIATED WITH THE USE OF MEDICATIONS FOR THE TREATMENT OF CHRONIC PAIN:



1. Conduct an assessment of all prescribed and over-the-counter medications used by the participant, including medical cannabis use.
2. Assign scores based on the different medication subclasses listed in the above table.
3. Sum these scores to obtain a total score.
4. Utilize this new continuous variable as an outcome, a determinant, a confounder, or an effect modifier in your clinical or epidemiologic research projects.

TO CITE OR FOR MORE INFORMATION:

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/* SAS code for the calculation of MQS-4.0 total score for each patient
before or after an index date using medication claim data.

    Year: 2023
    Author: Hermine L. Nguena N.


PDIP_Data_MQS: dataset that will be used for calculating the MQS-4.0
total score. This dataset contains information on prescription claims
and the index date.

surv_data: dataset containing survey data or other type of data,
including an index date (e.g., date of survey completion)

pharma_serv: Dataset containing all pharmaceutical information of each
patient (several lines per patient, each line corresponding to one
medication claim)

Variables

NOINDIV: patient ID
INDEX_DATE: index date
DATESERVICE: Date of claim
CLASSE_AHFS: AHFS (American Hospital Formulary Service) class of the
claimed medication
SMED_COD_DENOM_COMNE: Common Drug Name Code for the Medication
SMED_COD_FORME_MED: Code indicating the pharmaceutical form of the
medication
SMED_COD_DIN: Code corresponding to the Drug Identification Number
(DIN)

All M4_... variables, containing risk scores for each medication
subclass, are created using risk scores indicated in the Table 2 of the
article. */


data cohort.PDIP_Data_MQS;
merge cohort.surv_data (in=a keep=NOINDIV INDEX_DATE)
cohort.pharma_serv (in=b keep=NOINDIV DATESERVICE CLASSE_AHFS
SMED_COD_DENOM_COMNE SMED_COD_FORME_MED SMED_COD_DIN);
by NOINDIV_SRAP;
if a and DATESERVICE ge (INDEX_DATE-28) and DATESERVICE le INDEX_DATE;
/* 28 can be remplaced by the number of days before index date and -
can be remplaced by + if MQS-4.0 is calculated after index date*/
If classe_AHFS = '280804' AND SMED_cod_denom_comne in (47327,47346)
THEN M4_COX2= 5;/* NSAIDs—COX-2*/
Else M4_COX2 = 0;
If classe_AHFS = '280804' AND SMED_cod_denom_comne in (00143) THEN
M4_SALI = 5; /*NSAIDs—salicylates*/
Else M4_SALI = 0;
If classe_AHFS = '280804' AND SMED_cod_denom_comne NOT in
(47327,47346,00143) THEN M4_NSAID = 6; /*Other oral NSAIDs*/
Else M4_NSAID = 0;
If substr(CLASSE_AHFS,1,4)='8406' AND SMED_cod_denom_comne IN
(39042,00780,37768,46585,02548,38405,45448,47299,47884,09724,09737,0935
0,10881,17758,33413,38119,39055,04550,04563,04589,46390,46420,47598,087
62,47768) THEN M4_AINS_TOPIC= 2; /*NSAIDs—Topical agents*/
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Else M4_AINS_TOPIC= 0;
If substr(CLASSE_AHFS,1,4)='8406' AND SMED_cod_denom_comne = 45489 THEN
M4_TOPIC= 2; /* Various topical agents: Capsaicine*/
Else if SMED_cod_denom_comne  IN (40797 , 43345 , 43358 , 43930 , 46008
, 46050 , 46433 , 46481 , 46703 , 47750 , 05265 , 05278 , 05291 ,
18205) THEN M4_TOPIC= 2; /* Various topical agents: Lidocaine*/
Else M4_TOPIC=0;
If classe_AHFS = '280892' AND SMED_cod_denom_comne = 00039 THEN
M4_ACET= 2; /*Acetaminophen*/
Else M4_ACET= 0;
If substr(CLASSE_AHFS,1,4)='2808' AND SMED_cod_denom_comne IN
(47567,38496,46037,46168) THEN M4_ACET_OP= 6;/* Acetaminophen in
combination with an opioid*/
Else M4_ACET_OP= 0;
If classe_AHFS ='280808' AND SMED_COD_FORME_MED IN
(01827,02001,02262,02552,00203) THEN M4_OP_C= 8; /* Short-acting opioids
*/
Else M4_OP_C= 0;
If classe_AHFS = '280808' AND SMED_COD_FORME_MED IN
(00145,00435,05133,05162,05569,05570,05580,05592,05596,05597,05598,0560
0,05602,05603,05604,05611,05621,05622,05623,05624,05625,05643,05677,056
85) THEN M4_OP_L= 8; /* Long-acting opioids*/
Else M4_OP_L= 0;
If classe_AHFS = '280808' AND SMED_cod_denom_comne IN (47654,47860)
THEN M4_OP_IRN= 6; /* Opioids associated with a norepinephrine reuptake
inhibitor */
Else M4_OP_IRN= 0;
If classe_AHFS = '280812' AND SMED_cod_denom_comne IN (38847,44528)
THEN M4_ANTA_OPIAC= 6; /* Partial opioid receptor agonizts*/
Else If classe_AHFS = '990003' AND SMED_cod_denom_comne = 47835 THEN
M4_ANTA_OPIAC= 6;
Else M4_ANTA_OPIAC= 0;
If substr(CLASSE_AHFS,1,4)='2810' AND SMED_cod_denom_comne IN
(47725,47846) THEN M4_OP_ANTA_OPIAC= 6; /* Opioids in combination with
an opioid receptor antagonist*/
Else M4_OP_ANTA_OPIAC= 0;
If classe_AHFS = '281292' AND SMED_cod_denom_comne IN
(47080,47100,47229,47463,47571,38951,39393,44073) THEN M4_ANTICON_gaba=
5; /* Anticonvulsants—Calcium channel blockers (gabapentinoids)*/
Else M4_ANTICON_gaba=0;
If classe_AHFS = '281292' AND SMED_cod_denom_comne IN
(01404,47110,47430,47847,47875,47957) THEN M4_ANTICON_sodium= 6; /*
Anticonvulsants—Sodium channel blockers*/
Else M4_ANTICON_sodium=0;
If classe_AHFS = '2812 92' AND SMED_cod_denom_comne NOT IN
(47080,47100,47229,47463,47571,38951,39393,44073,01404,47110,47430,4784
7,47875,47957) THEN M4_ANTICON_other= 6; /* Anticonvulsants—Other*/
Else M4_ANTICON_other= 0;
If classe_AHFS = '281604' AND SMED_cod_denom_comne   IN (47118,47714)
THEN M4_ANTIDEP_IRSN= 4; /* Antidepressants—SNRIs*/
Else M4_ANTIDEP_IRSN=0;
If classe_AHFS = '281604' AND SMED_cod_denom_comne   IN
(45504,45630,45633,47061,47317,47553) THEN M4_ANTIDEP_ISRS= 4; /*
Antidepressants—SSRIs*/
Else M4_ANTIDEP_ISRS=0;
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If classe_AHFS = '281604' AND SMED_cod_denom_comne   IN (43137,47093)
THEN M4_ANTIDEP_5_HT2= 4; /* Antidepressants—SSRIs and 5-HT2 receptor
antagonists */
Else M4_ANTIDEP_5_HT2=0;
If classe_AHFS = '281604' AND SMED_cod_denom_comne   IN (47408) THEN
M4_ANTIDEP_NetS= 4; /* Antidepressants—Specific noradrenergic and
serotonergic */
Else M4_ANTIDEP_NetS=0;
If classe_AHFS = '281604' AND SMED_cod_denom_comne   IN
(00429,00442,02522,03198,04784,06578,08294,09906,14781,37443) THEN
M4_ANTIDEP_tri = 5; /* Antidepressants—Tricyclics*/
Else M4_ANTIDEP_tri=0;
If classe_AHFS = '281604' AND SMED_cod_denom_comne   IN
(07280,09698,42058,47005,47285) THEN M4_ANTIDEP_other= 4; /*
Antidepressants—Miscellaneous*/
Else M4_ANTIDEP_other=0;
If classe_AHFS = '281608' THEN M4_ANTIPSY= 6; /* Antipsychotics*/
Else M4_ANTIPSY= 0;
If classe_AHFS  IN ('281204','282404') THEN M4_BARB= 8; /* Barbiturates
*/
Else M4_BARB= 0;
If classe_AHFS IN ('282408','281208') THEN M4_BENZO= 8; /*
Benzodiazepines*/
Else M4_BENZO= 0;
If classe_AHFS = '282492' AND SMED_cod_denom_comne IN
(01703,43047,47912,04706,06045,08177,42058,45609) THEN M4_ANXIO_SEDAT=
6; /* Various anxiolytics, sedatives, and hypnotics */
Else M4_ANXIO_SEDAT= 0;
If classe_AHFS= '122004' THEN M4_MYO_central= 5; /* Centrally acting
skeletal muscle relaxants */
Else M4_MYO_central = 0;
If classe_AHFS= '122012' THEN M4_MYO_gaba= 5; /* GABA (gama-aminobutyric
acid)-derivative skeletal muscle relaxants */
Else M4_MYO_gaba= 0;
If classe_AHFS IN ('122008','122092') THEN M4_MYO_divers= 4; /*
Miscellaneous muscle relaxants */
Else M4_MYO_divers= 0;
If SMED_cod_denom_comne = 42838  THEN M4_CANNABINOIDS= 6; /* Synthetic
cannabinoids (under prescription)*/
Else M4_CANNABINOIDS= 0;
If classe_AHFS = '283228' THEN M4_ANTIMIGRAINE_5HT1= 4; /* Antimigraine
agents—5HT-1 receptor agonizts (triptans) */
Else M4_ANTIMIGRAINE_5HT1= 0;
If classe_AHFS= '283292' AND SMED_COD_DIN  IN (02497859,02509474) THEN
M4_ANTIMIGRAINE_CGRP= 4; /* Antimigraine agents—CGRP antagonists */
Else M4_ANTIMIGRAINE_CGRP= 0;
If classe_AHFS = '283292' AND SMED_COD_DIN  NOT IN (02497859,02509474)
THEN M4_ANTIMIGRAINE_divers= 5; /* Antimigraine agents—Miscellaneous */
Else M4_ANTIMIGRAINE_divers= 0;
If substr(CLASSE_AHFS,1,4)= '6804' AND SMED_cod_denom_comne IN
(02197,02587,03952,46420,06175,07956) THEN M4_CORTICO_O= 7; /*
Corticosteroids—Oral */
Else M4_CORTICO_O= 0;
If classe_AHFS = '240816'   AND SMED_cod_denom_comne = 10751 THEN
M4_CLON= 5; /*Clonidine*/
Else M4_CLON= 0;
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If classe_AHFS = '240404' AND SMED_cod_denom_comne = 44970 THEN M4_MEX=
6; /*Mexiletine*/
Else M4_MEX=0;
run;

*Intermediate MQS-4.0 score for each line (several line per patient);
data cohort.PDIP_Data_MQS;
set cohort.PDIP_Data_MQS;
MQS_4.0_int=
M4_COX2+M4_SALI+M4_NSAID+M4_AINS_TOPIC+M4_TOPIC+M4_ACET+M4_ACET_OP+M4_O
P_C+M4_OP_L+M4_OP_IRN
+M4_ANTA_OPIAC+M4_OP_ANTA_OPIAC+M4_ANTICON_gaba+M4_ANTICON_sodium+M4_AN
TICON_other+M4_ANTIDEP_IRSN+M4_ANTIDEP_ISRS
+M4_ANTIDEP_5_HT2+M4_ANTIDEP_NetS+M4_ANTIDEP_tri+M4_ANTIDEP_other+M4_AN
TIPSY+M4_BARB+M4_BENZO+M4_ANXIO_SEDAT+M4_MYO_central
+M4_MYO_gaba+M4_MYO_divers+M4_CANNABINOIDS+M4_ANTIMIGRAINE_5HT1+M4_ANTI
MIGRAINE_CGRP+M4_ANTIMIGRAINE_divers+M4_CORTICO_O+M4_CLON+M4_MEX;
run;

/* If the same medication (SMED_cod_denom_comne) is claimed more than
once within the study period for a patient, then consider it only once
*/
proc sort data=cohort.PDIP_Data_MQS;
by NOINDIVSMED_cod_denom_comne;
run;

data cohort.PDIP_Data_MQS;
set cohort.PDIP_Data_MQS;
by NOINDIV SMED_cod_denom_comne;
if first.SMED_cod_denom_comne;
run;

proc sort data=cohort.PDIP_Data_MQS;
by NOINDIV_SRAP;
run;

/*MQS-4.0 total score for each participant (one line per patient)*/

data cohort.PDIP_Data_MQS; set cohort.PDIP_Data_MQS;
 retain MQS_4.0;
  by NOINDIV_SRAP;
  if first.NOINDIV then do;
    MQS_4.0=0;
  end;
MQS_4.0+ MQS_4.0_int;
if last.NOINDIV_SRAP;
run;


/*To check MQS-4.0 distribution*/
proc means data=cohort.PDIP_Data_MQS N mean std Q1 median Q3 min max;
var MQS_4.0;
run;

** For patients covered by public drug insurance plan, but with no
claims during the study period, consider MQS-4.0 = 0 ***;
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Supplementary Appendix 2 - Growth Mixture Modelling

Model fit indices tables

Table legend:
[1] 1 = linear (straight line); 2 = linear + quadratic (u-shaped curve/parabola) components; 3 = linear + quadratic + cubic components [2] BIC: Bayesian information criterion NA: not applicable
* One or more groups in the model had less than 5% of participants
** Entropy < 0.8
*** Lowest proportion of individuals per group with posterior probability group ≥ 0.8 **Bold text:** Model which best fits the data and respected all criteria (lowest BIC absolute value among trajectory groups that respected the 5% criteria as well as entropy ≥ 0.8 and highest proportion of individuals per group with posterior probability group ≥ 0.8)

Model fit indices for MQS-4.0 risk score trajectories in the whole study sample

Number of trajectories	Trajectory shape 1	Entropy	BIC 2 (n=8,760)
1	1	NA	1171065.0
1	2	NA	1158975.0
1	3	NA	1158981.0
2	1	0.9416529	1162049.0
2**	2	0.6905794	1151421.0
2**	3	0.6905768	1151436.0
3	1	0.9316713	1156299.0
3**	2	0.7687867	1148024.0
3**	3	0.7687912	1148049.0
4	**1**	**0.8583271**	**1150711.0**
4***	2	0.8266736	1143696.0
4***	3	0.8552526	1143785.0
5**	1	0.7892655	1149201.0
5*	2	0.7926603	1141657.0
5*	3	0.8470322	1142057.0
6*	1	0.8019192	1147982.0
6*	2	0.7529791	1141961.0
6*	3	0.7914570	1141514.0

Model fit indices for trajectories of the number of analgesics and co-prescribed medications in the whole study sample

Number of trajectories	Trajectory shape 1	Entropy	BIC 2 (n=8,760)
1	1	NA	19946502.1
1	2	NA	19946502.1
1	3	NA	19946502.1
2	1	0.9568665	615718.8
2	2	0.9568659	615731.0
2	3	0.9668690	615742.6
3	1	0.9861390	489198.1
3	2	0.9861651	489206.9
3	3	0.9861782	489228.7
4	1	0.9694729	457213.2
4	2	0.9694953	457172.0
4	3	0.9694593	457206.6
5	1	0.9532880	444880.0
5	**2**	**0.9535563**	**444799.4**
5	3	0.9534806	444846.1
6*	1	0.9402202	441117.6
6*	2	0.9403927	441041.7
6*	3	0.9534806	441100.5