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Supplementary Material

Article Title: Novel Quality Control Metric for the Pharmacotherapy of Major Depressive Disorder: Measuring Guideline Concordance and Its Impact on Symptom Severity

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1. Appendix 1 Guideline Concordance Algorithm (GCA-8)

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Appendix 1 - Guideline Concordance Algorithm (GCA-8)

The eight criteria that form the GCA-8 are first derived from general practice guidelines common to many major depressive disorder (MDD) treatment guidelines then, where specifics are needed, from the 2016 Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines (*e.g.*, which drugs are first-line) or the work of Stahl* (*e.g.*, specific dose ranges); Additional thresholds (*e.g.*, gaps between treatments) were decided upon by our research team using distributional information from Penn State Psychiatry Clinical Assessment and Rating Evaluation System (PCARES) registry and clinical experience. The algorithm is focused on MDD pharmacotherapy but does not address all use scenarios for every available drug. Future adjustments may be needed. Several data pre-processing steps may be necessary for the application of this algorithm to electronic medical record data, some steps are described below.

Drug (Rx) classification with respect to MDD:

- First-line: agomelatine, bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mianserin, milnacipran, mirtazapine, paroxetine, sertraline, venlafaxine, and vortioxetine.
- Second-line: amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, levomilnacipran, moclobemide, nefazodone, protriptyline, quetiapine, selegiline, trimipramine, and vilazodone.
- Third-line: isocarboxazid, lurasidone, maprotiline, nortriptyline, paliperidone, phenelzine, reboxetine, and tranylcypromine.
- Adjunctive/augmentation therapies: aripiprazole, brexpiprazole, buspirone, lithium, lamotrigine, methylphenidate, olanzapine, pindolol, and quetiapine.
- Bupropion and quetiapine were excluded due to being monotherapies. Cariprazine and ketamine were considered experimental/under study and were not included for PCARES.

Multipurpose drug classifications:

- Doxepin: if prescribed at a dose ≤ 10 mg (threshold based on insurance coverage; the typical dose is 6 mg daily for sleep disorders) and the patient has an ICD-10 code for a sleeping disorder, the drug is considered to be used for the sleep disorder. Doxepin is included as a second-line with other tricyclic antidepressants.
- Duloxetine: if prescribed with an ICD-10 code for fibromyalgia, the drug is considered to be used for the fibromyalgia. Duloxetine can be prescribed for generalized anxiety disorder but is assumed to be targeting MDD.
- Milnacipran: if prescribed and an ICD-10 code for fibromyalgia is present, the drug is not prescribed for MDD.
- Paroxetine: if prescribed and the patient has an ICD-10 code for an anxiety disorder, it is considered to be prescribed for anxiety and if the dose is > 62.5 mg, it is prescribed for other conditions.
- Risperidone: if prescribed at a dose > 3 mg, the drug is not considered to be related to the treatment of psychiatric disorders; if the dose is ≤ 3, the drug is considered adjunctive.
- Trazodone: if prescribed at a dose ≥ 150 mg, the drug is considered a second-line treatment for MDD; if it is prescribed at a dose < 150 mg and the patient has an ICD-10 code for a sleep disorder, the drug is considered to be prescribed for the sleep disorder; if it is prescribed at a dose of < 150 mg and there is no ICD-10 code for a sleep disorder, the drug is assumed to be prescribed as an augmenting therapy.

Given the above codes, if a drug is a first-line, second-line, third-line, adjunctive, or augmenting therapy, and not likely to be prescribed for a comorbid condition, it is considered "related" to the treatment of MDD for this algorithm. Classifications may overlap and not all classifications are represented. All MDD-related drugs in a combination treatment were evaluated where applicable; the more complex the regimen the greater the risk of misclassification for some criteria. Because drug priority could not be assigned (*i.e.*, which drug is primary), drugs prescribed within a given visit were sorted alphabetically. Drug classification was completed using the American Hospital Formulary Service Index.

Classification of MDD and selection of the baseline visit date:

- The "baseline" visit date was set to the MDD diagnosis date nearest to, and within one year prior and one year after, the registry encounter visit. The indicator for recurrent MDD is intended to help capture treatments that would be logical for those who have had MDD in the past and may try treatments not recommended for those with first-time episodes.
- Non-recurrent MDD was classified using the following ICD-10 codes: F32.0, F32.1, F32.2, F32.9, F33.0, F33.1, F33.2, or F33.9
- Recurrent MDD was classified using F33.0, F33.1, F33.2, F33.9, F33.40, F33.41, or F33.42

Identifying switching and continuances:

- Medications were compiled into visit-by-visit entries such that one row represented the related drugs prescribed on that visit. Subsequently, "switching" was identified as events in which the treatment at a given visit was characteristically different from the most recent prior combination regardless of doses. A "modification" also included dose changes. Dropping a drug from a combination treatment was not considered a switch in the treatment approach. Because of the structure of electronic medical record data, it was helpful to collapse consecutive treatments with no pause between them, termed a "continuance" of treatment; identical drugs that were prescribed consecutively at different doses were considered separate entries. This step was done by taking only the earliest start date for a drug at a given dose and the latest stop date. The continuance indicator was coded as 0 at the baseline date and at the date of the first prescription (if different).

Classifying treatment gaps:

- Treatment gaps were assessed as a gap of > 30 days and < 180 days between the stop date of a given drug and the order date of the next drug in the dataset. A gap of > 30 days precluded a "continuance." Gaps > 180 days were considered indicative of relapse and therefore not treated as a gap in treatment for one given episode. Drug entries where the order date was more than 270 days after the visit were considered errors and were dropped.

Median thresholds:

- Researchers can decide whether to set the threshold to 1) zero to evaluate all discordance, 2) the median value for the full study sample (assuming it is not 0) to account for some population or provider level discordance that may be a product of separate processes (*e.g.*, local resources), or 3) the median for those who experience the relevant events (*i.e.*, among those who do switch at least once).

Average episode duration:

- Participants who are in treatment longer are not only more likely to have more complex clinical status but also more likely to try multiple treatment approaches and thus have greater potential to fail additional treatment guidelines. As a result, careful adjustment for MDD episode duration and visit frequency is important. The difference in days between visit dates with consecutive ICD-10 codes for active depression was calculated to obtain the sum of days with an active episode. The summed durations were then divided by the number of episodes (per codes for remitted depression: F32.4, F32.5, F33.40, F33.41, or F33.42) to obtain the average episode duration per patient in days. Those without remission events had their average episode duration set to the full time spent in the registry. Those with an average duration of less than 30 days were set to missing.

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Starting GCA-8 score
All patients start with a maximum score of 8.

+8

Criterion 1
The first medication in the treatment window

Using the baseline date, assess the first drug prescribed in the given study window. If two or more medications are prescribed first, as long as a first-line (or second-line in the case of recurrent MDD) is included the event is considered concordant. Adjunctive and augmenting therapies should not be considered.

- The patient had non-recurrent depression and initially received a received a second-line or third-line medication. → -1
- The patient had recurrent depression and their first medication was a third-line medication. → -1
- The patient's first treatment was concordant or there was no eligible event. → -0

Criterion 2
The initial second-line medication is not after more than two first-line medications.

Tally the number of unique first-line drugs that are prescribed before the initial second-line drug.

- The patient's number of unique first-line drugs was greater than two. → -1
- The patient's initial second-line treatment was concordant or there was no eligible event. → -0

Criterion 3
The initial third-line medication is after a second-line medication.

If a patient receives a third-line medication during the treatment window, that medication should be tried after a second-line medication was tried. For this criterion, as long as a second-line drug was tried, it does not matter whether it directly precedes the third-line drug.

- The patient's initial third-line medication is not after a second-line medication. → -1
- The initial third-line treatment was concordant or there was no eligible event. → -0

Criterion 4
The Rx dose is increased to the recommended maximum before switching (# of discordant events ≤ median) and the total number of switches is not more than the median (# of switches ≤ median).

This criterion considers only drugs related to MDD treatment and excludes tapering from the evaluation of the maximum dose tried. The highest dose tried for a given combination should be evaluated against the recommended maximum (per CANMAT and Stahl) for the same drug. To simplify the algorithm, if any drug in a multi-drug approach reaches its maximum dose before a switch event, the criterion is considered satisfied.

Evaluate the median number of switch events and the median number of times failing to reach the maximum dose before switching.

- The patient had a switch event count that exceeded the median or the median number of events where the maximum dose was not reached before a switch was exceeded. → -1
- The patient's regimen did not exceed the median number of switch events or the median number of events where the maximum dose was not reached before a switch. → -0

Criterion 5
Treatment duration should be at least four weeks per Rx, two weeks per dose (# of discordant events ≤ median; excluding tapering), with an average gap of fewer than 31 days and a limited number of gaps (# of gaps ≤ median).

The duration of treatments was set using prescription start and stop dates. Tapering periods shorter than two weeks were not treated as discordant. There is a risk of misclassification for complex treatment approaches that involved multiple drugs.

Evaluate the median number of events where a drug or dose was prematurely changed and the median number of treatment gaps (discontinuities in treatment greater than 0 days and less than 180 days) in the sample.

- The patient had a drug or dose switched prematurely more times than the median, an average treatment gap of 31 days or more, or a number of treatment gaps greater than the median. → -1
- The patient had no more premature drug and dose switches than the median, an average treatment gap of 30 days or less, and a number of treatment gaps less than or equal to the median. → -0

Criterion 6
Treatment should be modified by changing the dose (tapering excluded) or adding an adjunctive/augmenting drug, before switching to a new med. (# of discordant events ≤ median).

The two treatment steps before a switch were evaluated to determine whether the same drug was prescribed but a dose was modified. Dropping drugs, tapering doses, or ultimately switching back to a drug was not considered discordant.

Evaluate the median number of events where the drug or dose was not modified prior to switching.

- The patient's regimen had more failures to modify than the median threshold. → -1
- The patient's regimen was modified appropriately. → -0

Criterion 7
The Rx combo is without notable drug-drug interactions (# of interactions ≤ median).

Important drug-drug interactions were identified using CANMAT and literature,[*,**] primarily those occurring via the cytochrome P450 pathway. Those that may induce serotonin syndrome were also included. A variant of the "continuance" indicator was used for this step to ignore different doses of the same medication (as opposed to treating them as separate entries).

Evaluate the median number of potential drug-drug interactions.

- The number of potential drug-drug interactions exceeded the median threshold. → -1
- The number of potential drug-drug interactions is less than or equal to the median threshold. → -0

Criterion 8
The visit frequency should be at least three visits every six months.

A simple tally of visits within six months was used to establish whether a patient met the concordance criteria in one year.

- The number of visits was less than three in six months. → -1
- The number of visits was at least three in six months. → -0

Final GCA-8 score

[*]Stahl SM. Prescriber's Guide. Cambridge University Press; 2020. doi:10.1017/9781108921275

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