Trends in pharmacotherapy for anxiety and depression during COVID-19: a North York area pilot study

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Abstract

Introduction: During the COVID-19 pandemic, with the implementation of social distancing regulations, there is increased concern around the mental health of the general population, including depression and anxiety. Mental health prescribing trends in Canada during COVID-19, at the time of writing, have not been investigated.

Methods: This pilot study collected refill information of 365 patients from an independent community pharmacy in North York, Ontario to compare (1) initiation, (2) dose change, (3) dispensing frequency, and (4) defined daily dose of first-line antidepressants as defined by the Canadian Network for Mood and Anxiety Treatments and other select medications, including Z-drugs and benzodiazepines. Data from January 1 to May 31, 2019 were compared with data from January 1 to May 31, 2020.

Results: The number of newly initiated antidepressant and antianxiety medications during the COVID-19 pandemic was not significantly affected compared to the same months in the prior year (Z=-1.149, p=0.251). Upon investigation of logistic regression, age was significantly correlated to antidepressant initiation in the year prior (p=0.038) whereas it was not during COVID-19, which may represent an increase in antidepressants in the younger population. There was a significant difference in the number of dose changes, which occurred between the two years, showing significantly more increases and switches of therapy (p=0.008) during COVID-19. There was significantly more frequent dispensing of benzodiazepine tablets (Z=2.402, p=0.016) in the first five months of 2020 compared to those of 2019. There were no statistically significant changes in the number of defined daily doses.

Discussion: There are shifting trends in mental health prescribing. This result is concerning during a time when accessing appropriate mental health care is significantly impacted. This study emphasizes the need for benzodiazepine deprescribing due to the increase in benzodiazepines dispensed and the risk of misuse, tolerance, and dependence with long-term benzodiazepines.

Introduction

In late 2019, multiple COVID-19 disease (Sars-CoV-2) outbreaks were being reported in Wuhan, China. Months later, in early 2020, the World Health Organization declared the COVID-19 virus outbreak a pandemic.

In order to slow the onslaught of individuals infected with the virus, many countries implemented lockdowns and the closure of public spaces, local stores, and recreational parks, as well as mandated social distancing regulations. Some of the key features of self-management of depression including exercise, yoga, acupuncture, and adequate sleep are likely to have faced massive disruption due to these changes.[1] Other aspects of mental wellbeing which are likely to have been impacted include social interactions, in-person psychotherapy appointments, and all-time high unemployment rates.[2] Since social distancing has been mandated, Canadians have reported a worsening of their mental health and many have reported feeling anxious or "on-edge".[3]

The medications included in this study were the first-line treatment options from the 2016 Canadian Network for Mood and Anxiety Treatments (CANMAT).[1] Two of the classes were selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). SSRIs and SNRIs, the most commonly prescribed antidepressant medications, are typically taken daily and increase the neurotransmitter serotonin in the brain to improve or stabilize mood. Another included class were benzodiazepines (BDZs), which may be taken daily, but are more often taken "as needed". BDZs exert their anxiolytic effect through the GABA receptor. Non-Benzodiazepine Benzodiazepine Receptor Agonists (BZRAs) or "Z-drugs" were also included, which are used for sedation in anxiety or insomnia.

It has been established in the literature that non-clinical factors play a role in antidepressant and antianxiety medication use: social isolation, unemployment, and loneliness are associated with higher use of anxiolytics and antidepressants.[4,5] Those who live alone have higher antidepressant use rates than those living with someone.[6] In the elderly, social disconnectedness increases perceived social isolation and in turn, increases depression and anxiety symptoms.[7]

These studies have shown consistent results in their establishment of a pronounced effect on General Anxiety Disorder-7 score, Symptom Check List-90 index score and Zung Self-Rating

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Depression Scores during COVID-19.[8,9] Higher prevalence of generalized anxiety symptoms, depressive symptoms, and sleep quality disturbances have been demonstrated to disproportionately affect the younger populations during this time.[8] The majority of the studies published used online questionnaires and survey data to establish mental health trends. It is not clear from these studies whether the changes were resulting in more diagnoses and prescribing or whether it was simply a phenomenon observed through self-reporting.

One of the few publications which investigated the effects on prescribing is a trend report by Express Scripts published in April 2020. This report showed an increase in claims of antidepressant, anxiolytic, and hypnotic/sedative medications by 18.6%, 34.1%, and 14.8%, respectively, from January 2020 to the week that COVID-19 was declared a pandemic.[10] This report did not disclose any data after March 15, 2020. This report also did not compare the 2020 trends to any baseline trend.

What the body of literature cannot tell us at this point is any Canadian trends in the prescribing and dispensing of mental health medications. It also cannot tell us what trends occurred in medication dispensing in the months following the initial pandemic announcement. "Trends" specifically referred to the (1) initiation, (2) dose or therapeutic change, (3) dispensing frequency, and (4) defined daily dose (DDD) of selected mental health medications. To come to this assessment, OVID and SCOPUS were used as search engines. Keywords used with the corresponding search methods can be found in the supplementary appendix. Relevant studies were selected based on author discretion.

Methods

Research ethics approval was obtained in June 2020 from the University of Toronto Faculty of Pharmacy Undergraduate Research Ethics Committee. This pilot study was conducted using data collected from the pharmacy software system at a community pharmacy located in North York, Ontario. All data from the pharmacy software system on fill rates of one or more of the selected medications at this community pharmacy between January 1, 2019 to May 31, 2020 were included.

The collected data were used to investigate the pharmaceutical trends of select antidepressant, anxiolytic, and hypnotic/sedative medications dispensed during that timeframe. The list of selected medications consisted of SSRIs and SNRIs, as they are the preferred initial therapy for treatment of anxiety and depression, and all first-line treatment options from the 2016 CANMAT that are available in Canada.[1] BDZs and Z-drugs were also included, as both these classes of medications are commonly used to treat acute anxiety or sleep disorders. The full list of medications investigated are presented in Appendix 1. The study population consisted of patients who filled one or more of the listed medications presented in Appendix 1 between January 1, 2019 and May 31, 2020, with no exclusions. These included both "regular users", defined as those who filled all their prescriptions at this pharmacy, and "occasional users", defined as those who filled only some of their prescriptions at this pharmacy.

In accordance with Division (1) clause 2.C of the Personal Information Protection and Electronic Documents Act (PIPEDA), informed consent was not required as all information collected was de-identified and used solely for the purpose of this study.

Data Collection

Data on (1) initiation, (2) dose or therapeutic change, (3) dispensing frequency, and (4) DDD of select medications were collected, and data from January 1 to May 31, 2019 were compared to data from January 1 to May 31, 2020. The age and gender of patients who filled one or more of the selected medications were collected for analysis of trends as well. In this study, gender referred to that which was listed in the pharmacy operating system, which was either indicated on the individual's Ontario Health Card or self-identified by the individual.

Initiation of Selected Medications

Initiation of a medication was defined as the patient's first fill of the medication at the pharmacy since October 2018. Data were collected from as far back as October, such that three-month supply data extending to January 2019 could be captured to assess for dose changes. Only changes made beginning January 1, 2019 were taken into account for the analysis. The number of initiations was measured monthly across the first five months of this year and the previous year to observe any trends which may be consistent with the initiation of antidepressants during the implementation of social distancing measures.

Changes of Selected Medications (dose and drug)

Dosage change of a medication referred to the increase or decrease in strength of the medication and/or a change in the therapy. It was calculated as the number of dose and/or therapeutic changes per month.

Dispensing Frequency of BDZs

Fill frequency was measured as the quantity of pills of BDZs dispensed monthly. This was chosen as an independent measure from DDD for the BDZ medications due to the commonly prescribed "as needed" nature of this class.

DDD

The DDD of five classes of mood and antianxiety medications were measured. Medications were grouped as SSRIs, SNRIs, BDZs, Z-drugs, and others in order to determine their consumption.[11]

Confounding Variables
Changes in prescribing patterns

Prescribing patterns by clinicians in the area can influence pharmaceutical trends observed in the community pharmacy. Principal investigators reviewed specialties and recent moves into and out of the area that could potentially affect prescribing patterns (i.e. new mental health clinics opened up within a 10 km radius of the pharmacy). No significant changes to practice in the area were found.

Table 1. Sociodemographic variables of sample population

Variable	n (%) or mean (SD)
Gender, n (%)	
Female	223 (61)
Male	142 (39)
Age, mean (SD), years	46.78 (18.24)

Sociodemographic Variables

In the Bayview Village neighbourhood where this community pharmacy is located, there was an average household size of 2.22 persons, and a population density of 4,195 per square km.[12] In terms of cohabitation and loneliness considerations, 50.2% of individuals over 15 years of age were married in this neighbourhood and 22.2% of individuals were seniors living alone.[12] With respect to other social factors, 59.7% were immigrants, with 64% having a mother tongue which was not English.[12] The median family income in this neighbourhood was $67,355, with 24.5% living in poverty.[12] Such demographics can be considered by those hoping to extrapolate these pilot data to other populations.

Analysis

Outcome variables were presented as mean ± SD of 2019 and 2020. IBM SPSS software was used to analyze trends of data collected. Comparison of the following outcomes, (1) number of new prescriptions per month received at the pharmacy, (2) number of dose changes (increase and decrease) and drug changes per month, (3) total number of pills of BDZs per month, and (4) DDD of SSRI, SNRI, BDZs, Z-drugs, and others per month for each month from January to May of 2019 and 2020, was conducted.

Results

Investigators extracted medication fill history between June 25 to 28, 2020 from community pharmacy software. Data were collected from October 2018 to May 2020, inclusive. Data from this entire period were collected due to a software hindrance, which did not allow for the collection of two independent periods of 5 months. However, only two periods of five months (January 1 to May 31, 2019 and January 1 to May 31, 2020) were used for analysis. A total of 365 prescription fill results were collected. These were de-identified by assigning participant numbers and entered into IBM SPSS software for analysis.

Outcomes
Sociodemographic variables of patients

Data were collected from patients with a mean age of 46.78 ± 18.24 years, with 61% of patients identified as female (Table 1).

Initiation

The monthly number of initiations from the first five months of this year were not statistically significantly different from the number of initiations during the first five months of the previous year (17.0 ± 14.92, 25.8 ± 17.54, respectively, Z=-1.149, p=0.251) (Figure 1). There was no more than one initiation per unique patient per year.

The logistic regression model of 2019 showed that age was significantly correlated to the likelihood of antidepressant initiation (p=0.038), with increasing age being associated with an increased likelihood of initiating an antidepressant. The logistic regression model of 2020 showed that age was not correlated (p=0.624) (Table 3).

In 2019 and 2020, gender was not significantly correlated to the likelihood of antidepressant initiation (p=0.082, p=0.699, respectively) (Table 3).

Changes to Selected Medications (dose and drug)

The number of monthly dose changes during the COVID-19 pandemic was statistically significantly different compared to the number of dose changes from the previous year (3.2 ± 0.837, 0.80 ± 0.837, respectively, z=-2.546, p=0.008). There were significantly more increases and switches of therapies per month during the COVID-19 pandemic compared to the same months in the previous year (2.8 ± 0.2, 0.6 ± 0.244, respectively, z=-2.739, p=0.008). The maximum observed number of dose changes or drug switches per patient per year was 2.
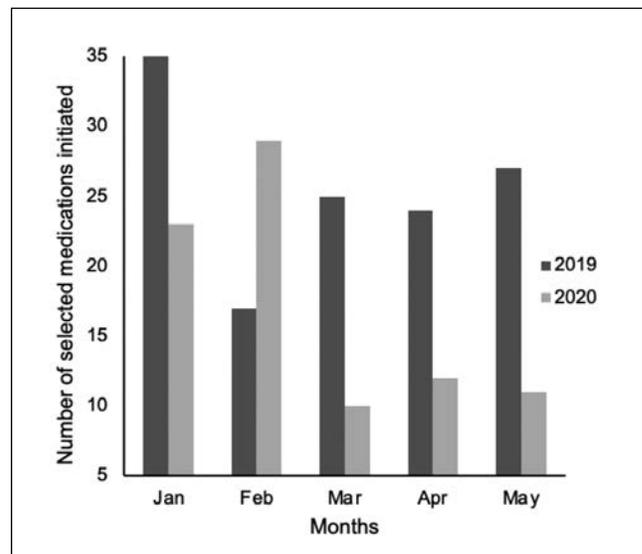

Figure 1. Number of antidepressants initiated per month in 2019 (dark grey) and 2020 (light grey).

Table 2. Mean ± SD and Mann-Whitney (z-score and p-value) of defined daily dose of medications dispensed from January to May of 2019 and of 2020

Medication category	Jan to May 2019 (mean ± SD)	Jan to May 2020 (mean ± SD)	Z (p)
SSRIs	2353.10 ± 251.56	2044.30 ± 586.76	-0.940 (0.347)
SNRIs	577.61 ± 149.35	744.34 ± 258.00	-0.946 (0.344)
Benzodiazepines	247.29 ± 109.62	351.20 ± 57.68	-1.567 (0.117)
Z-drugs	498.53 ± 164.95	523.40 ± 184.78	-0.104 (0.917)
Others	518.70 ± 228.21	466.10 ± 217.87	-0.731 (0.465)

Table 3. Binomial logistic regression of the initiation of antidepressants in 2019 and 2020

2019	β	SE	p
Age[a]	0.013	0.006	0.038*
Gender	0.434	0.249	0.082
2020	**β**	**SE**	**p**
Age[a]	-0.004	0.007	0.634
Gender	-0.105	0.272	0.699

[a]Average age of patients who filled an antidepressant in 2019 and 2020 was 49.96 ± 1.83 years and 45.78 ± 2.31 years, respectively.
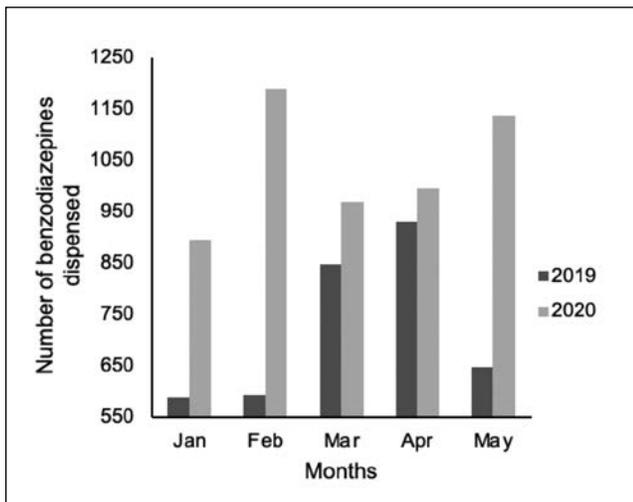
* p < 0.05

Figure 2. Dispensing frequency of benzodiazepines per month from January to May 2019 (dark grey) and 2020 (light grey).

Table 4. Binomial logistic regression of the volume of benzodiazepine tablets dispensed in 2019 and 2020

2019	β	SE	p
Age	0.39	0.015	0.010*
Gender	1.669	0.538	0.002*
2020	β	SE	p
Age	0.029	0.012	0.018*
Gender	-0.785	0.457	0.086

* p < 0.05

Table 5. Defined daily dose of selective serotonin reuptake inhibitor (SSRI), serotonin and norepinephrine reuptake inhibitor (SNRI), benzo-diazepine (BDZ), Z-drugs, and others calculated from January to May in both 2019 and 2020

Months	SSRI	SNRI	BDZ	Z-drugs	Others
Jan-19	2055.5	777.15	230.4667	449.333	863.5
Feb-19	2203.5	411.9	174.375	242	312
Mar-19	2503.5	559.8	154.3125	645.333	607
Apr-19	2634	673.275	431.1875	634.667	324
May-19	2279	465.9	246.125	521.333	487
Jan-20	2763	996	305.8375	474.333	418.5
Feb-20	2516.5	1032.5	428.4875	833	574.5
Mar-20	1552	559.8	283.2125	350.333	787
Apr-20	1420	673.275	370.9875	432	271.5
May-20	1970	460.125	367.45	527.333	279

Dispensing Frequency

There was a 43.7% increase in BDZ dispensing in the first five months of this year compared to the year prior. The number of BDZ tablets dispensed monthly during the COVID-19 pandemic was statistically significantly higher compared to the previous year (1037.4 ± 122.24, 721.6 ± 156.87, respectively, z=-2.402, p=0.016) (Figure 2).

The logistic regression model showed that age was significantly correlated to the quantity of BDZs dispensed in 2019 and in 2020 (p=0.010, p=0.018, respectively), with increasing age being associated with an increased likelihood of dispensing a BDZ (Table 4). The average age of patients who dispensed a BDZ in 2019 and 2020 was 52.37 ± 2.11 years and 52.8± 2.37 years, respectively.

In 2019, gender correlation was statistically significant (p=0.002). However, during COVID-19, gender was not significantly correlated (p=0.086) with BDZ dispensing. In 2019 and 2020, females received 69.23% and 53.84%, respectively, of all dispensed BDZs.

DDD

The DDD of SSRIs, SNRIs, BDZs, Z-drugs, and others in 2019 and 2020 were calculated (Table 2) and a Mann-Whitney test was conducted (Table 5). The test did not show a statistically significant change in DDDs dispensed for any of the medication classes.

Confounding Variables
Changes in Prescribing Patterns

Within a 10 km radius, there were five doctor's offices, two hospitals, and three medical clinics. Based on a review of specialty services and practice updates online, there were no practice changes between January 2019 and May 2020 in the area that were considered to have a significant impact on the prescribing patterns of mental health medications.

Discussion

The observed increase in dose changes, specifically significantly more increases and switches of therapy and anxiolytic dispensing during COVID-19, is in agreement with the previously reported literature on mental health trends and reinforces the concerns researchers and health care providers have raised during this pandemic.[3,8,9]

There was an age correlation of initiating pharmacotherapy in 2019, but lack of age correlation during COVID-19. This lack of correlation during COVID-19 likely reflects an increase in initiations in the younger population. This is consistent with a previous study, which established that mental health was disproportionately impacting the younger population.[8] Half of the world's students are affected by the closure of educational institutions, and recent graduates are affected by the significant rates of unemployment and economic disruption.[2,13] This finding is important when considering where public health resources should be allocated and how the mental health of the younger population can be supported.

There was no significant increase in overall antidepressant initiations, which was inconsistent with trends reported by Express Scripts in the beginning of 2020, where they saw an increase in antidepressant medications.[3] This may be explained by the closure of clinics and decreased number of in-person doctor's appointments, limiting access, which particularly may impact the elderly.[14] Technological barriers can also prevent access to telemedicine and virtual appointments.[14]

There was a significant increase in BDZ dispensing and a significant increase in antidepressant dose or drug change. This is consistent with Canadians self-reporting more anxiety and worsening mental health and with the trend report by Express

Scripts, which observed an increase in claims for anxiolytics during the first three months of 2020.[3,10]

There was a lack of significant increase in BDZ initiation, and an increase in BDZs dispensed. This may represent a worsening in the mental health of patients who were previously diagnosed with and treated for depression and/or generalized anxiety disorder during the pandemic. In the available studies, the pandemic has been shown to possibly play a role in the relapse of anxiety symptoms.[15]

The increase in BDZ dispensing during the pandemic reinforces the rising concern health care providers and researchers have expressed about the mental health crisis in elderly individuals during COVID-19.[15,16] In addition, age was positively correlated with BDZ dispensing during this time and in the year prior. There is also concern regarding the risk of adverse effects associated with BDZ use and its appropriateness in this age group. BDZs are commonly reported to increase the risk of falls and fractures in the elderly, and thereby increase morbidity and mortality.[17,18] BDZs are indicated for short-term treatment of anxiety, but are often misused. The long-term use of BDZs is associated with harm and can increase the risk of dependence and substance abuse.[19,20]

Health care professionals' awareness of these shifting trends will be important moving forward. First, appropriate follow-up on this medication therapy is critical for its safety. This includes monitoring for adverse reactions following prescribed dose increases and therapy changes as well as increased consumption of "as needed" medications. Deprescribing will also be an important tool moving forward. Physicians and pharmacists must pay attention to the ongoing appropriateness of pharmacotherapy.

The awareness of these trends is also critical for the consideration of how these trends will affect future mental health phenomena. This study hopes to emphasize the importance of deprescribing BDZs in the near future, as the pandemic evolves. Evidence-based guidelines for deprescribing BDZs have been established. Discussion of the manifestation of anxiety, how a dependence on BDZs will be avoided, and nonpharmacologic strategies to cope with these episodes will benefit patient care.

Limitations

Data were collected from one community pharmacy in North York, Ontario. Results are representative of the socioeconomic, ethnic, age, and cultural factors of the patients of this pharmacy, but may not be representative of the population at large. Results may disproportionately represent prescribing practices of the doctors who are located closer to the pharmacy. Results may disproportionately represent dispensing practice and clinical services of an independently owned pharmacy. Limitations of DDD are that it is not always reflective of standard doses in clinical practice, and specialized populations, such as adolescent and pediatric populations, do not receive "standard" doses. Limitations exist as to the "baseline" year established as 2019. Further data from previous years would help to reinforce a baseline of psychiatric medication prescriptions dispensed.

Future directions

Our pilot study informs areas where larger population research should be conducted. This includes prescribing patterns of BDZs and age association in a larger population during COVID-19, as the situation evolves.

Pharmacotherapy trends are one manifestation of the decline in mental health control. Research is warranted to investigate the shifting control of other manifestations, including eating disorders, substance abuse, and self-harm.

It is generally recommended that longer-acting BDZs be prescribed as rescue treatments in anxiety disorders rather than shorter-acting agents, as there is a decreased comparative likelihood of developing a dependence. Future research should seek to understand which BDZs are being prescribed at the highest rates during COVID-19 to determine whether inappropriate short-acting therapy trends must be addressed.

Further, it is recommended by the Canadian Agency for Drugs and Technologies in Health (CADTH) that BDZs be used as a short-term treatment for generalized anxiety disorder.[19,20] Future studies and guidelines must ensure that either deprescribing or adequate follow-up is in place.

Appendix 1

List of Medications our Study Looked at [ATC in brackets]

SSRI
- Citalopram [N06AB04]
- Escitalopram [N06AB10]
- Fluoxetine [N06AB03]
- Fluvoxamine [N06AB08]
- Paroxetine [N06AB05]
- Sertraline [N06AB06]

SNRI
- Desvenlafaxine [N06AX23]
- Duloxetine [N06AX21]
- Milnacipran [N06AX17]
- Venlafaxine [N06AX16]

Benzodiazepine
- Alprazolam [N05BA12]
- Bromazepam [N05BA08]
- Chlordiazepoxide [N05BA02]
- Clobazam [N05BA09]
- Clonazepam [N03AE01]
- Clorazepate [N05BA05]
- Diazepam [N05BA01]
- Flurazepam [[N05BA01]
- Lorazepam [N05BA06]
- Midazolam [N05CD08]
- Nitrazepam [N05CD02]
- Oxazepam [N05BA04]
- Temazepam [N05CD07]
- Triazolam [N05CD05]

Z-drugs
- Zolpidem [N05CF02]
- Zopiclone [N05CF01]

Other
- Bupropion [N06AX12]
- Mirtazapine [N06AX11]
- Vortioxetine [N06AX26]

Supplementary Appendix

Literature Search Strategy
Keywords
1. SSRI OR selective serotonin reuptake inhibitor OR benzo* OR antidepressant
2. COVID OR COVID19 OR COVID-19 OR Sars-CoV-2 OR coronavirus OR pandemic OR quarantine OR social distanc* OR isolation
3. initiat* OR precrib* OR take OR taking OR consum* OR trend
4. Dose adj3 increase OR Dose adj3 change OR Dose adj3 escalat* Dose adj3 adjust*
5. Medication refill* OR prescription refill* OR medication fill* OR fill* behaviour OR refill behaviour OR as adj1 needed OR prn OR rescue
6. Depression OR anxiety

Search Strategy (MEDLINE Database)
- 1 and 2 and 3
- 1 and 2 and 4
- 1 and 2 and 5
- 2 and 6

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