Therapeutics Initiative
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THERAPEUTICS LETTER 152
January 2025

Should antidepressants be prescribed to people with substance use issues?

PLAIN LANGUAGE SUMMARY

If someone has anxiety, feels depressed, or has other mental health problems, stopping or reducing use of alcohol or drugs (substance use) often improves their mental health.

Antidepressant medicines like sertraline or escitalopram usually do not help in these cases. Sometimes, these medicines may worsen substance use.

Research shows that:

- Mental health symptoms like anxiety and depression are common in people who drink or use other drugs. These symptoms are often caused or worsened by the substances themselves.
- Stopping or reducing drinking and other drug use usually improves these symptoms dramatically.
- Antidepressants often don't work well in people with substance use problems. They can sometimes increase the urge to use drugs and alcohol, leading to worse results.

Why don't antidepressant medicines work well in substance use problems?

- Limited benefits: research studies show that antidepressants such as sertraline, fluoxetine, venlafaxine, and trazodone generally do not improve psychological symptoms in people with substance use problems.
- Possible harms: in some people, taking antidepressant medicines can lead them to drink more alcohol or use more drugs. This may be because of their effects on the brain's reward system.
- Research gaps: many studies of antidepressants excluded people who had substance use problems, so the results may not apply to these types of people.

Better treatment choices:

The best way to help people with substance use problems and psychological symptoms is to focus on reducing or stopping drinking and drug use. This often leads to a big improvement in mental health. Treatments that can work include:

1. Effective medicines for substance use disorders:
   - Alcohol use disorder: acamprosate can help people who want to stay sober.
   - Tobacco use disorder: nicotine replacement therapy and varenicline can help people quit smoking.
   - Opioid use disorder: opioid agonist therapy can help.
2. Counselling and support: talking with a therapist or joining a support group can help with reducing substance use and improving mental health.
3. Specialist help: if withdrawal symptoms or ongoing substance use become too hard to manage, addiction medicine clinics or telemedicine resources can provide extra support.

What should patients and doctors know about this?

- Psychological symptoms like anxiety or depression often improve dramatically when people quit or drink less and use fewer other drugs, without the need for antidepressant medicines.
- If antidepressants are considered, the prescriber and patient should be aware that benefits are unproven, and monitor closely for worsening substance use.
- Effective treatments for substance use disorders (e.g., medications for alcohol or smoking) should be used more often.

This method focuses on dealing with the root causes of the symptoms, leading to better long-term results for both mental health and substance use.

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Avoid serotonergic antidepressants for people with alcohol and other substance use disorders

ABSTRACT

Background: People with substance use disorders (SUDs), including alcohol use disorder (AUD), often experience symptoms such as anxiety, depression, and insomnia. These symptoms are often connected to the biological and social effects of substance use and withdrawal. Historically, treatment was conservative, guided by expected remission of symptoms following substance reduction or abstinence. However, prescribing of serotonergic antidepressants (SSRIs, SNRIs, SARIs) in this population has increased, despite limited evidence supporting their efficacy and the potential risks of worsening substance use.

Aims: This *Therapeutics Letter* considers whether antidepressants should be prescribed to patients with SUDs, particularly AUD. Findings from systematic reviews suggest that commonly prescribed serotonergic antidepressants offer no significant improvement in psychological symptoms and some RCTs demonstrate worsening substance use outcomes. This Letter also highlights the underutilization of proven treatments for SUDs, such as psychological interventions and medications like acamprosate and varenicline.

Recommendations: Clinicians are advised to avoid prescribing serotonergic antidepressants in patients with SUDs and concurrent mental health disorders. Rather, treatment should prioritize evidence-based pharmacological and non-pharmacological strategies for reducing or abstaining from substance use, which can often alleviate associated psychological symptoms. If an antidepressant is prescribed, despite lack of evidence for benefit, advise the patient of the evidence gap and monitor closely for increasing substance use. Shifting resources toward evidence-based therapies and patient support systems could improve outcomes in this population.

Keywords: Alcohol Use Disorder; Antidepressive Agents; Anxiety; British Columbia; Cannabis Use Disorder; Cocaine-Related Disorders; Depression; Mental Disorders; Selective Serotonin Reuptake Inhibitors; Serotonin and Noradrenaline Reuptake Inhibitors; Serotonin Antagonists; Sleep Initiation and Maintenance Disorders; Substance-Related Disorders; Substance Withdrawal Syndrome; Tobacco Use Disorder; Trazodone.

Multiple experts and primary care clinicians reviewed the draft of this Therapeutics Letter for factual accuracy, and to ensure it is relevant to clinicians.

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Avoid serotonergic antidepressants for people with alcohol and other substance use disorders

Vignette: *A 21-year-old student books an office appointment for help with anxiety, insomnia, and low mood. He describes a distressing and unprovoked panic attack at a supermarket till, and also says he often awakens from sleep, feels "depressed" and fatigued, and has difficulty concentrating in class. When you inquire, he says he drinks about "3-6 beer" and smokes cannabis every evening. He also smokes half a pack of cigarettes/day, and "often" uses cocaine and MDMA on weekends. He has no prior history, nor family history, of anxiety or depression. Having seldom prescribed medications for alcohol or other substance use disorders, you plan to review recent guidelines. But since he complained about anxiety and low mood, and having often prescribed antidepressants, you wonder whether to start one now.*

Summary and conclusions

- **Symptoms of depression and anxiety are common in people with substance use disorders (SUDs). Research demonstrates that rapid resolution is common with a reduction of substance use or abstinence.**
- **Commonly prescribed serotonergic antidepressants, including selective serotonin reuptake inhibitors (SSRIs), venlafaxine and trazodone, do not improve common psychological symptoms in people with substance use disorders, including alcohol use disorder. They increase substance use in some patients.**
- **Avoid serotonergic antidepressants for people with substance use disorders and concurrent mental health issues. If you do prescribe – despite lack of evidence for benefit – monitor closely for antidepressant-induced increased substance use or pathological intoxication.**

Introduction

This *Therapeutics Letter* considers whether we should prescribe antidepressants to people with alcohol use disorder (AUD) and other substance use disorders (SUDs). Because alcohol use disorder is the most prevalent and well-studied SUD, this Letter focuses on the evidence from AUD. It also explores what is known about use of antidepressants in people with non-alcohol SUDs.

In 2023 the *Canadian Medical Association Journal* published a national guideline, funded by Health Canada, on the clinical management of high-risk drinking and AUD.[1] **The new guideline discourages routine prescription of SSRIs and highlights the limited benefit and potential harms of other commonly prescribed antidepressants for people with AUD.**

This *Letter* employs recent conventional nomenclature for antidepressant drug classes: selective serotonin reuptake inhibitor (SSRI), serotonin and noradrenaline reuptake inhibitor (SNRI), serotonin-antagonist and reuptake inhibitor (SARI). But we do not intend the use of this nomenclature to imply that drug mechanisms, or their ultimate effects in the brain, are well understood.[2]

Alcohol and other substances engender mental health problems, and vice versa

People who use psychoactive substances including alcohol, cannabis, tobacco and "recreational" drugs (e.g., amphetamines, cocaine, opioids), often complain of psychological symptoms such as sleep disturbance, anxiety, and low mood.[3] These may be caused or exacerbated – in people with prior mental health problems – by the biological and social effects of psychoactive substance use. For example, increased autonomic nervous system activity is a hallmark of alcohol withdrawal.[1] Thus many patients experience mild alcohol withdrawal as anxiety and insomnia.

Alcohol is itself a depressant, and psychosocial consequences of alcohol use – such as guilt and shame – can foster loneliness and depression. Cannabis, amphetamine, cocaine, opioids, and even tobacco use are also associated with elevated rates of depression, anxiety and other mental health challenges.[3-6]

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A flight from evidence-based practice?

Historically, best practice for patients with active substance use disorder required caution about assigning mental illness diagnoses such as anxiety or depression - **as most symptoms would remit with abstinence alone.**[3,5,6] Consistent with modern DSM-5-TR diagnostic criteria, many clinicians delayed any pharmacological treatment of depression and anxiety until the underlying impacts of substance use were excluded or addressed. However, it is often difficult for primary care clinicians to help their patients access effective psychosocial or psychological treatments for SUDs. Efforts to manage symptoms with medication are now common.[7]

Increasing antidepressant use in BC for any SUD

The high prevalence of SUDs in British Columbia is well known. Less recognized is the increasing likelihood that a patient diagnosed with a substance use disorder will be treated with an antidepressant. TI pharmacoepidemiologists derived Figures 1-3 from analysis of the anonymized BC Medical Services Plan and PharmaNet databases.[8] **Figures 1-3 reveal increased new dispensing of antidepressants** to people diagnosed with SUDs in BC from 2002 through 2023. New (incident) dispensing is defined as dispensing of an antidepressant within 30 days of a SUD diagnosis – to a person for whom there was no such dispensing within the prior 365 days. Trazodone, escitalopram (displacing racemic citalopram) and sertraline now predominate. The increase in trazodone dispensing from 2013-2014 likely reflects substitution of trazodone for benzodiazepines (BZDs) after greater recognition of the harms of benzodiazepines in this population – and regulatory advice against combining BZDs with opioids.

Could antidepressants worsen SUD outcomes? An old/new idea?

Over 20 years ago, warning signs began to emerge that treatment of certain SUDs with selective serotonin reuptake inhibitors (SSRIs) **might increase substance use**. For instance, randomized controlled trials (RCTs) of 3 different SSRIs reported from 1996 to 2004 demonstrated **increased drinking** in "type B" (higher severity/risk) AUD.[9-11] A subsequent trial reported in 2011 (N=134) explored whether a genetic polymorphism of the serotonin transporter gene 5-HTTLPR may predispose a person with AUD to either reduced or increased consumption of alcohol during treatment with sertraline.[12] The investigators observed that because the genotype potentially implicated in SSRI-induced heavier alcohol use is more common than the potentially beneficial allele, about twice as many people with AUD would be "*adversely affected*" by a SSRI. They concluded that the "*widespread use of antidepressants (in people with AUD) suggests that the findings reported here are relevant to a substantial proportion of the U.S. population.*"[12]

Industry-funded RCTs of antidepressants usually **did not assess alcohol use**. In 2019, researchers at the Nordic Cochrane Centre reported their inability to evaluate long-term effects of SSRI treatment on excessive alcohol consumption.[13] Furthermore, 80% of published efficacy RCTs of antidepressants for major depression from 1995 through 2014 **excluded people with AUD or a SUD.**[14] **Thus, most RCT results are not generalizable to people with "dual diagnoses" of depression and SUD.** The psychiatrists

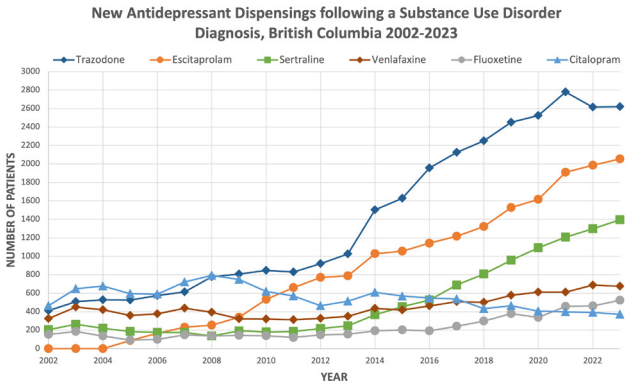

Figure 1: New dispensing 2002-2023 of the most popular antidepressants to British Columbians diagnosed with any SUD (alcohol, opioid, amphetamine, cocaine, cannabis, tobacco, hallucinogens, sedative/hypnotics, anxiolytics, tranquilizers, barbiturates, and unspecified drug-induced mental or sleep disorders). In 2002, 1,961 British Columbians initiated an antidepressant within 30 days of a SUD diagnosis. By 2023, this increased 4-fold to 7,788 people. BC's population increased 35% over the same 21-year interval.

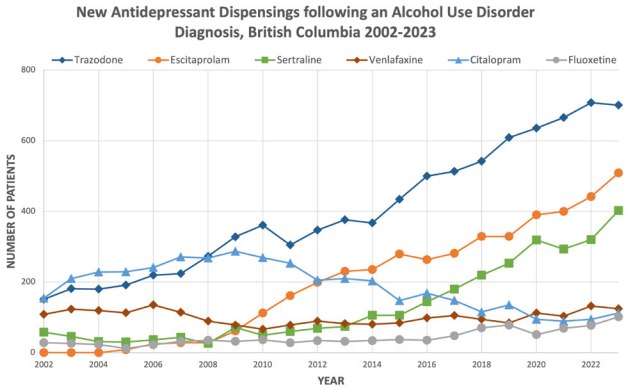

Figure 2: New dispensing 2002-2023 of the most popular antidepressants to British Columbians diagnosed with AUD. In 2002, 693 British Columbians initiated an antidepressant within 30 days of an AUD diagnosis. By 2023, this increased by nearly 3-fold to 1,976 people, also far exceeding population growth.

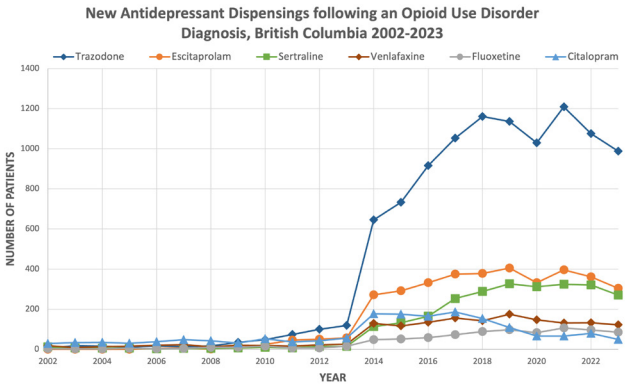

Figure 3: New dispensing 2002-2023 of the most popular antidepressants to British Columbians diagnosed with OUD. In 2002, 84 patients initiated an antidepressant within 30 days of an OUD diagnosis. By 2023, this increased 22-fold to 1,851, over 60 times faster than population.

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who reviewed these RCTs suggested that product monographs reflect this routine exclusion of patients with a SUD from pre-approval RCTs.[14]

A range of RCTs involving various SUDs, plus case report series, document the **emergence or worsening of substance use problems, including pathological intoxication, during antidepressant treatment.**[9-12,15-20] Clinicians therefore need to be vigilant for worsening substance use problems after prescribing a potential culprit drug. Fortunately, when an antidepressant is stopped or switched, increased alcohol use is reported to be reversible.[18]

Scant evidence that antidepressants benefit people with SUDs

Of equal concern for routine prescribing of antidepressants to people with SUDs is the evidence suggesting lack of benefit – especially for the drugs most often prescribed. This is particularly compelling for SSRIs (e.g., citalopram/escitalopram, fluoxetine, sertraline), SNRIs (e.g., venlafaxine), and SARIs (e.g., trazodone). The evidence gap applies to SUDs with or without "co-morbid" diagnoses of depression or anxiety.

A 2015 Cochrane systematic review (SR) concluded that "*the evidence-base for the effectiveness of medication in treating anxiety disorders and comorbid alcohol use disorders is currently inconclusive.*"[21] A subsequent 2018 Cochrane SR of antidepressants in people with co-occurring depression and alcohol dependence found only "*low-quality evidence supporting clinical use of antidepressants,*" when all antidepressants including tricyclic antidepressants were considered. The authors noted that "*most positive effects were no longer significant when studies with high risk of bias were excluded.*"[22]

The efficacy of serotonergic antidepressants appears particularly questionable. Canadian authors of a 2020 meta-analysis of 32 RCTs of drug treatment for major depressive disorder in people with concurrent SUDs concluded that SSRIs "*either alone or in combination with relapse prevention medications such as naltrexone, had no significant effect on depressive symptoms.*"[23] The investigators' conclusion is striking: "***The lack of efficacy of SSRIs found in our study. . .challenges the clinical rationale for using SSRIs for the treatment of depression in people with MDD and addiction comorbidity.***"[23]

Do SSRIs increase alcohol use in AUD?

Dopamine is the neurotransmitter most implicated in substance use disorders, but serotonergic neurotransmission is also believed to play a role.[24] Yet many systematic reviews of serotonergic antidepressants, including the Cochrane SRs cited above, **selectively omitted studies in which serotonergic antidepressants were prescribed specifically for a SUD.**[21,22]

Several RCTs document clear harms of SSRI antidepressants in AUD. For example, 6 RCTs utilizing 4 SSRIs vs placebo (citalopram, fluoxetine, fluvoxamine, sertraline) demonstrated potential for increased alcohol use in some people.[9-12,15,25]

The largest relevant RCT funded by the U.S. National Institutes of Health (N=184) – reported only in abstract format – could not replicate earlier findings of a possible genetic risk for worse outcomes under SSRI treatment.[25] But participants who wanted to abstain from drinking and were randomized to citalopram 37-60 mg/d **used more alcohol** than those who received placebo.[25] The largest RCT yet conducted (N=265) was a Canadian trial of citalopram 40 mg/d vs placebo in people with AUD, of whom 49% also had mild depression or anxiety.[15] **Worse drinking outcomes in the citalopram group** led the investigators to conclude: "***The use of SSRIs among depressed and nondepressed alcohol-dependent individuals early in recovery, prior to the onset of abstinence, may be contraindicated.***"[15]

How do antidepressants affect tobacco, cannabis, OUD, or other SUDs?

A 2023 updated Cochrane SR confirmed efficacy of bupropion for **tobacco smoking cessation** (and less so, nortriptyline), but it found no evidence in favour of SSRIs or venlafaxine.[26] However, in 2 poorly reported RCTs of fluoxetine vs placebo for smoking cessation (N=247 and N=989), fluoxetine appeared to increase relapse to smoking at the conclusion of treatment.[27,28]

For **cannabis use disorder**, a 2021 SR and network meta-analysis found that in small RCTs, none of escitalopram, fluoxetine, venlafaxine, or vilazodone (a "serotonin modulator") improved abstinence.[29] However, vilazodone (40 mg/d) increased the severity of cannabis craving.[29] A 12-week RCT (N=103) showed that the SNRI venlafaxine at 225-375 mg/d increased cannabis consumption and total adverse effects. The investigators concluded: "*For depressed, cannabis-dependent patients,* ***venlafaxine-extended release does not appear to be effective at reducing depression and may lead to an increase in cannabis use.***"[17]

For **opioid use disorder**, a 2010 Cochrane SR of pharmacological treatment for depression during opioid agonist treatment found only "low quality" studies. The only statistically significant comparisons to placebo identified were in reference to tricyclic antidepressants.[30] The review also demonstrated more overall study drop-outs (in studies with low risk of bias) and more serious adverse events requiring study withdrawal, in those randomized to antidepressants vs placebo.[30]

For **stimulant disorders**, experimental evidence also demonstrates potential for harm from SSRIs. In methamphetamine dependence, results of a 12-week RCT (N=229) using sertraline 100 mg/d vs placebo (+/- contingency management) led the authors to deem sertraline "*contraindicated.*"[16] An increased propensity to relapse after completing 6 weeks of treatment in the sertraline groups (13/61) vs placebo (5/68) appeared to relate to sustained craving for methamphetamine.[31] As early as 1992, a RCT (N=155) randomized cocaine users to fluoxetine (20 mg, 40 mg, or 60 mg/d) or placebo, finding that fluoxetine appeared to worsen treatment success - possibly dose-dependently.[32] Authors of a 12-week RCT (N=68) comparing fluoxetine 40 mg/d with placebo for people with cocaine dependence and major depression found that abstinence from cocaine was significantly lower in the fluoxetine group, with no commensurate benefit on depression.[33]

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The 2011 Cochrane SR of antidepressants for cocaine dependence and problematic cocaine use found no benefit of antidepressants vs placebo on depression outcomes. Participants treated with SSRIs were more likely to drop out or be withdrawn from treatment due to adverse events.[34]

What about trazodone?

Trazodone has become an extremely common off-label treatment for insomnia, including in people with AUD and OUD.[35,36] BC data show a steep increase in its incident dispensing for all SUDs (Figures 1-3). This probably reflects substitution of trazodone for BZDs as sedative/hypnotics, especially after regulators and guidelines discouraged prescription of BZDs starting about 2012. But the increased popularity of trazodone is also **not evidence-based**. Some experimental evidence suggests that increased drinking during trazodone treatment might relate to its active metabolite, meta-chlorophenylpiperazine (m-CPP). The latter has been observed to increase "*pharmacologically induced alcohol craving.*"[37-39]

From 2002 to 2006, US investigators screened 2,437 alcohol-dependent patients with sleep disturbance for a 12-week RCT comparing trazodone with placebo for insomnia after detoxification from alcohol in a short-term inpatient program.[40] Only 7% (N=173) of these were not also drug-dependent or receiving psychotropic medication, and thus eligible for a trial of isolated AUD and insomnia. Most were male, and many unhoused, unemployed or depressed. Participants randomized to trazodone 50-150 mg/d vs placebo reported slightly improved sleep during treatment, but used more alcohol.[40] Three months after trazodone was stopped, increased drinking persisted, but not sleep improvement. UpToDate acknowledges this trial in its discussion of insomnia treatments for people with SUDs, as well as the scant other evidence supporting the popularity of trazodone.[41] It recommends "close monitoring of drinking" for patients with AUD.[41]

In people taking methadone maintenance for OUD, 1 RCT (N=137) compared sleep quality and polysomnography over 6 months with trazodone 50-150 mg/d vs placebo. The investigators found that: "Trazodone did not improve subjective or objective sleep in methadone-maintained persons with sleep disturbance."[36]

How can we best treat patients now?

The efficacy of psychological interventions is less tested in RCTs than pharmacotherapy. However, it has been known for decades that abstinence, or reduction of substance use, often dramatically improves psychological symptoms.[3,5,6] Even quitting smoking benefits mental health with a magnitude of effects similar to those of antidepressant drugs on mood and anxiety.[4]

Evidence-based pharmacotherapy and some psychological interventions also improve outcomes substantially in alcohol, opioid, and tobacco use disorders.[1,42-44] Yet such proven treatments are still underutilized. For instance - in contrast with the popularity of antidepressant prescriptions for AUD – increased prescription of medications **shown to improve outcomes in AUD** could be expected to improve clinical results.[1,45]

Evidence-based change is needed

Even in people without alcohol or other substance use disorders, reappraisal of industry-funded antidepressant RCTs suggests that **benefits of antidepressants have been overstated**.[46] In 2019, Nordic Cochrane Centre investigators reanalyzed a highly cited network meta-analysis of 522 antidepressant trials (N=116,477 patients) published in 2018.[47] The Danish reanalysis identified a mean difference between antidepressants and placebo of only 1.97 points (95% CI 1.74-2.21) on the 52-point Hamilton Depression Rating Scale (HDRS).[48] This average effect is well below the change in HDRS detectable by clinicians or patients as meaningful improvement. The authors concluded that for uncomplicated depression in adults, "***it is unclear whether antidepressants are more efficacious than placebo***." Similar reservations led physicians, researchers, patient representatives and politicians in the United Kingdom in 2023 to call for government commitment to reverse the increase of antidepressant prescribing to the general population.[49]

Reducing unwarranted and potentially harmful prescription of antidepressants to people with SUDs may represent a significant practice change for some clinicians, including specialists. But this widely shared recommendation opens the door for clinicians and policy-makers to emphasize funding for more effective models of treatment. In May 2024, with input from the Canadian Psychiatric Association and the Canadian Academies of Adolescent and Geriatric Psychiatry, Choosing Wisely Canada advised against routine use of antidepressants in AUD.[50]

Vignette resolution: *Your patient sought help for psychological symptoms likely caused by biological or social effects of his use of multiple psychoactive substances. Given his limited insight into how alcohol, nicotine, cannabis and cocaine cause or worsen his anxiety, insomnia and low mood, you offer a series of follow-up appointments with a goal to help him substantially reduce, or ideally stop using psychoactive substances. To begin, you refer him to substance use counselling, and suggest:*

- *acamprosate for AUD (NNT~11 for abstinence over 12-52 weeks)[51]*
- *nicotine replacement and varenicline (NNT~13 over 6-12 months for smoking cessation)[44]*

If he develops troublesome withdrawal or struggles with ongoing substance use despite your assistance, you could refer him for support through an addiction medicine clinic or obtain additional support from telemedicine resources including British Columbia's 24/7 Addiction Medicine Clinician Support Line bccsu.ca/24-7

Data References and Disclaimer

The BC Ministry of Health approved access to and use of BC data. The following data sets were used: PharmaNet, MSP Payment Information File, Discharge Abstract Database, National Ambulatory Care Reporting System: PharmaNet. All inferences, opinions and conclusions drawn in this manuscript are those of the authors and do not reflect the opinions or policies of the data stewards.

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