ABRUPT STOP

Managing discontinuation syndrome associated with psychoactive medications

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An awareness of discontinuation syndrome (DS) and familiarity with the medications that cause it are important when assessing and providing pharmaceutical care for mental health patients. This patient population is more prone to abrupt stoppage of one or more of their medications due to adverse effects, the stigma associated with mental illness and medication cost, or simply once they "feel better," they tend to self-discontinue the medication. The purpose of this article is to enhance pharmacists' understanding of the causes, intricacies and incidence of DS, addressed from a biopsychosocial standpoint. As well, the article discusses the most common mental health medications with the potential to induce DS, the major factors contributing to the development of DS in the mental health population, prevention of DS, and approaches to the management of DS symptoms once they have developed.

What is DS?

DS is a condition in which the patient experiences adverse effects that result

from an abrupt discontinuation of a medication.[1] The term "discontinuation" is often used instead of "withdrawal" because withdrawal implies addiction or dependence.[2] Moreover, "withdrawal," especially in the context of addiction medicine, often includes hallmark features such as diaphoresis, tremor, tachycardia, monoclonus, anxiety, seizures and persistent drug craving. "Discontinuation," on the other hand, does not involve craving or drug-seeking behaviour and is more of a "rebound" effect.[3] Symptoms of DS generally begin within the first 24–48 hours after drug discontinuation or dose reduction and last for up to seven to 14 days, depending on the medication.[1] In some cases, adverse effects from discontinuation may persist longer, as seen with paroxetine.[4]

Medications associated with DS

While many medications can result in DS when they are abruptly stopped, this article focuses on the major classes of mental health medications that can cause DS:

- tricyclic antidepressants (TCAs)
- Selective serotonin reuptake inhibitors (SSRIs, e.g., paroxetine) and serotonin-norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine)
- Norepinephrine-acetylcholine serotonin selective agents (NaSSas) (i.e., mirtazapine)[5]
- Atypical antipsychotics (i.e., olanzapine, quetiapine, risperidone and clozapine)
- Benzodiazepines

An understanding and awareness of physical and psychological effects associated with stopping these medications is important because up to 30% of the population will require an agent in one of these classes in their lifetime for treatment of depression, generalized anxiety disorder, pain management, bipolar disorder or schizophrenia.

What causes DS?

DS may be characterized and identified as a poverty of receptor activity.[1,6] SSRIs, SNRIs, NaSSas, monoamine oxidase inhibitors (MAOIs) and TCAs have effects at serotonin, norepinephrine and/or acetylcholine receptors. This is a direct extension of their pharmacological activity and why they are effective as first- or second-line therapies in depression.[7] However, when any of these antidepressants is removed too abruptly, there is a lack of the neurotransmitter at the receptor, resulting in discontinuation syndrome with rebound physical and psychological sequelae.

Recognizing DS

One of the major challenges in recognizing psychoactive medication DS is the fact that symptoms often mimic the initial mental health condition being treated. As discussed above, however, DS can be distinguished from an underlying mental health problem because DS symptoms usually present within one to three days after discontinuation, whereas depressive symptoms usually only present two to three weeks after antidepressant medication is stopped. In clinical observation, the intended use of the antipsychotic (i.e., for bipolar disorder, schizophrenia, depression, psychosis) will determine the length of time required for the underlying psychiatric condition to manifest after the acute DS has subsided. Even with this diagnostic distinction, only 72% of psychiatrists and 30% of general practitioners had an understanding and knowledge of discontinuation syndrome and realized that their patients may experience these negative effects.[8]

Factors contributing to development of DS

Given that patients receiving mental health care have a higher incidence of lapses in therapy or treatment adherence due to medication cost, adverse effects (e.g., anticholinergic effects, sexual dysfunction, memory loss), stigma or other factors, community pharmacists have the opportunity to identify nonadherence early and help patients before negative outcomes result.[9] In addition, pharmacists should be cognizant of a number of medication-specific factors that are linked to DS (Table 1).

Table 1 MEDICATION-SPECIFIC FACTORS CONTRIBUTING TO PSYCHOACTIVE MEDICATION DISCONTINUATION SYNDROME[12]

- Genetic polymorphisms
- Pharmacokinetic and pharmacodynamic interactions
- Concurrent medications that may affect metabolism
- Shorter half-life of the medication
- Absence of active metabolites
- Higher "likeability index" or dependence liability of the medication
- Higher doses of the medication
- Longer duration of therapy with the medication

Nonadherence

Patients with mental health conditions have many challenges associated with taking their medication in a regular and timely way. Nonadherence in patients with mental health conditions is higher than in the general population, with up to 44% of depressed patients being nonadherent within three months,[10] and 75% of patients with schizophrenia being nonadherent at 18 months.[11] These high rates of nonadherence can be attributed in part to the factors listed in Table 2. Mental health patients are also at a disadvantage, since the etiology and clinical presentation of the disorders themselves may preclude the insight that would allow patients to make adequate choices and interventions regarding their medications.

Impact of DS on the patient

The impact of DS is multifaceted, with both short-term effects and longer-term sequelae. The impact must be seen from a biopsychosocial standpoint, taking into consideration biological, psychological and social changes, as well as the patient's perspective.

Biological

The short-term biological changes associated with DS are usually physiological in nature, where the patient presents with fever, irritability, nausea, insomnia, sensory changes (e.g., auditory or visual hallucinations) and headache.[12] Tics and movement disorders, up to frank catatonia, may also be present, especially with abrupt discontinuation of atypical antipsychotics.[7] After acute discontinuation syndrome, return of the underlying psychiatric conditions may occur,[13] while long term, possible neurobiological changes may be noted, such as atrophy of the hippocampal size and widening of the ventricle size in the brain, which enhances the probability of developing treatment resistance.

Psychological-social

Return of the underlying symptoms and the acute mental health and physiological distress add to the psychosocial burden of the patient in at least one functional area, including work, home or social life.[14] This may present as loss of work, increased sick time, and/or loss of or impact on personal or professional relationships. This could then extend to substance abuse, severe psychopathology and treatment resistance.[10,15]

Table 2 RISK FACTORS ASSOCIATED WITH NONADHERENCE TO MENTAL HEALTH MEDICATIONS[9,40,41]

Patient-related factors
Low socioeconomic index, older age, male sex, substance abuse, uneducated, medical co-morbidities, genetics, polymorphisms, stigma, religion

Illness-related factors
Lack of insight, manic symptoms, delusions, hallucinations, cognition changes, dementia, delirium

Clinician-related factors
Negative therapeutic alliance, stigma associated with mental illness, limited access to healthcare providers, lack of education about illness management and recovery structures (e.g., support groups)

Environmental factors
Medication cost, poverty, poor access to medical care, inadequate family support, poor access to community support networks (e.g., local mental health services, Canadian Mental Health Association), poor/inadequate housing

Treatment-related factors
Higher doses, polypharmacy, complicated regimens, multiple dosing times, adverse effects (primarily movement disorders, sexual side effects, weight gain), long time to onset of efficacy (e.g., antidepressants)

Medications and DS

Symptoms, mechanisms and management

Physiological dependence on mental health medications is a normal consequence of pharmacological receptor site activity.[1,6] Antidepressant DS may occur with TCAs, MAOIs, SNRIs and SSRIs. DS symptoms with these agents usually include flu-like symptoms, dizziness, fatigue, headache, insomnia, anxiety/agitation and rebound panic disorder.[16] Such symptoms usually start within a few days (at most) of treatment cessation, or rarely even when tapering a dose or when medications are added that are inducers of the cytochrome P450 system. DS usually subsides in a few days, especially if antidepressant treatment is restarted.[16]

SSRIs

Up to 30% of patients who stop SSRI treatment will experience DS.[7] Patients receiving an SSRI will have a persistent increased concentration of serotonin in the synapse, which results in a desensitization of the postsynaptic serotonin receptor by down-regulation. When an SSRI is discontinued, there is a temporary deficiency of serotonin in the synapse, which leads to the physical symptoms of DS.[6,15,17]

The individual SSRIs vary in their potential to cause DS when abruptly discontinued, with paroxetine most commonly associated with DS and fluoxetine the least likely.[6,18] Risk factors for developing DS with an SSRI include shorter half-life agents (e.g., paroxetine); therapy for more than four weeks; a history of emergent anxiety, DS or nonadherence; lack of active metabolites; and higher doses employed in therapy (e.g., for post-traumatic stress disorder).[19] The rationale for lack of active metabolites as a risk factor centres around the premise that active metabolites provide an equal or lower degree of serotonergic activity that

allows effects on the receptor beyond the time of the parent molecule. Since half-life plays such an important role in the development of DS with the SSRIs, proposed ways of preventing SSRI-related DS is to either gradually taper the SSRI or switch to fluoxetine when trying to discontinue an SSRI. Fluoxetine has such a long half-life (~9 days) that it self-tapers when it is stopped.[3,6,19]

SNRIs

DS with venlafaxine (an SNRI) often presents with mild symptoms (e.g., dizziness, headaches, nausea, agitation, anxiety) that last for a similar duration to that observed with SSRI-induced DS.[20] However, two case reports have described the development of suicidal ideation as part of the DS reaction following the abrupt stoppage of venlafaxine. In addition, four published case reports have described emergent psychosis (e.g., delusions, auditory hallucinations) or mania when venlafaxine was discontinued. The psychosis was severe enough in one case that the patient required long-term antipsychotic treatment until resolution.[20]

Given that venlafaxine has a short half-life and serotonergic effects, it is thought to induce DS in a manner similar to that described above for SSRIs.[20] While the risk for developing SNRI DS is greater with higher doses of venlafaxine and abrupt discontinuation, there have been case reports of DS occurring even with low-dose venlafaxine and gradual discontinuation of the drug. Therefore, although the usual recommendation is to gradually reduce the dose of venlafaxine when stopping it, some patients may demonstrate intolerance to stopping even a low dose of venlafaxine.[20] Clinically, in these patients we will reduce to the lowest possible dose of venlafaxine (e.g., 37.5 mg po daily). If even that intervention is not tolerated by the patient, a single dose of 10 mg fluoxetine will ameliorate the DS, due to fluoxetine's long half-life and active metabolites.

Finally, since suicidal ideation has also been observed (rarely) when abruptly discontinuing venlafaxine, clinicians may wish to monitor more carefully in order to identify patients at risk for abrupt discontinuation of their antidepressants and work to prevent abrupt discontinuation. They should also manage the DS more aggressively once it occurs, by reinstituting therapy or providing a longer-acting appropriate alternative.[21]

TCAs

TCAs inherently also have serotonergic activity. Consequently, it is believed that DS with TCAs involves the same mechanism as DS with SSRIs and SNRIs. However, it is important to note that TCAs also affect the cholinergic system. As a result, abrupt discontinuation of a TCA may also lead to signs of cholinergic rebound (e.g., parkinsonism, problems with balance).[16] Other symptoms of TCA-induced DS include lethargy, headache, tremor, sweating, insomnia, gastrointestinal upset, irritability and anxiety/agitation.

Similar to DS secondary to abrupt stoppage of an SSRI, risk factors for developing DS from discontinuing TCAs include higher dose, lack of active metabolites, use for a prolonged time, shorter half-life and history of substance abuse.[1]

Treatment of TCA-induced DS may include either restarting the medication and tapering it off slowly or invoking short-term use of anticholinergic agents (e.g., atropine or benztropine) if the patient is opposed to restarting the TCA.[3,16]

Four published case reports have described emergent psychosis or mania when venlafaxine was discontinued.

Antipsychotics

Antipsychotic DS was first identified in the late 1950s, when five out of 17 subjects in a clinical trial of the typical antipsychotic, chlorpromazine, were reported to develop DS symptoms.[22] Typical antipsychotics, although used less today, by virtue of their effects on the dopamine-acetylcholine balance are also associated with DS.[23]

Most atypical antipsychotic agents have some serotonin-dopaminergic antagonism and cases of DS have been reported with all of the atypical agents to varying degrees and presentation depending on the agent. The proposed mechanism of their therapeutic effects involves dopamine-D2 antagonism and potent serotoninergic (5-HT2) antagonism. In addition, antipsychotic drugs inherently have antagonistic effects at α-adrenergic, histaminergic and cholinergic receptors, with the degree of effect at each receptor varying according to the individual agent. The symptoms of DS can be predicted prospectively by receptor binding and affinity. The variation in receptor action among these agents also explains why a very specific DS is seen for each different atypical agent.[1] This (in theory) may be why risperidone is believed to have a higher incidence of tics and movement disorders among the atypical antipsychotics, as its dopamine/serotonin ratio most closely mimics that of a typical agent.

Risk factors for developing DS with an antipsychotic agent may include the following: higher dose, lack of active metabolites, usage for prolonged duration of time, and history of substance abuse.[1] Of the atypical antipsychotics, clozapine is most likely to produce a DS when abruptly stopped.[24]

Benzodiazepines

Benzodiazepines modulate the neurotransmitter activity of γ-aminobutyric acid (GABA) and interact with binding sites on the GABA receptor complex. This results in an increased receptor affinity for GABA,

with resultant sedation. When the benzodiazepine is abruptly stopped, there is a decrease in the inhibitory and sedative effects of GABA, as well as increased glutamate, which yields excitatory effects. Chronic use of benzodiazepines leads to adaptive changes, including GABA receptor down-regulation and increased glutamate. This contributes, in part, to the DS seen with benzodiazepines.[25]

When benzodiazepines are abruptly stopped, DS symptoms can last for weeks or months. They are most commonly seen with benzodiazepines that have a short or intermediate half-life. Reported symptoms include excessive anxiety, palpitations, insomnia, labile mood, restlessness, perceptual disturbances (e.g., vision, hearing), seizures, psychosis and delirium.[2,26-28] The development of seizures or psychosis is rare, but occurs more frequently in patients who have been taking a large dose of a benzodiazepine with a short or intermediate half-life for more than four months. The risk for seizure is also higher in an individual with a history of seizures or if the patient is also taking other medications that lower the seizure threshold.[28]

Non-benzodiazepines such as zolpidem (not marketed in Canada) or zopiclone have a very similar DS profile to the benzodiazepines. Symptoms include nausea, lightheadedness, dizziness, nausea, tachycardia, anxiety, and possibly seizures.[29,30]

In order to reduce the risk of DS, clinicians can consider selecting benzodiazepines with longer half-lives (e.g., diazepam, clonazepam) and gradually taper these agents over a few weeks when they are to be discontinued. When tapering, the first 50% of the dose can be more rapidly reduced than the last 50% of the dose. The final 50% of the dose should be reduced by 10% at five- to seven-day intervals, as this will result in a plateau period that helps the clinician distinguish between DS symptoms or a return of the underlying psychiatric condition.[28] Other tapering strategies include substituting a longer half-life benzodiazepine at equipotent doses. (The gold standard would be diazepam, which may not be indicated in all patients.) This new longer half-life benzodiazepine would be started at two-thirds of the equipotent dose and gradually tapered in 10% increments, or as tolerated by the patient.[31,32] One rule of thumb (used by the writer) is to decrease no faster than every 3.33 half lives (active metabolites included) plus 50%. For example, paroxetine has a half life of about 15–22 hours in the average adult and no active metabolites. Thus we would reduce the dose by 10% (or as tolerated by the patient) every 75–110 hrs. This allows steady state to be reached and the patient can be observed before the next reduction.

It is generally agreed that women should continue their antidepressants during pregnancy as the benefits outweight the risks. However, the newborn may be at risk for mild signs and symptoms of DS post-delivery.

Neonatal Serotonin DS

Whether to continue to treat depression during pregnancy is controversial. Evidence in the literature suggests that leaving depression untreated during pregnancy can increase the risk of miscarriage, prematurity, low neonatal assessment scores (APGAR scores) at birth, and negative effects on growth. It may also increase the risk of poor prenatal care, suicide ideation/attempts, postpartum depression and impaired mother-infant interactions.[33-36] Moreover, some women may substitute the antidepressants with drugs of abuse or alcohol, which will have an even greater negative impact on the fetus and newborn.[33]

Consequently, it is generally agreed that women should continue their antidepressants during pregnancy as the benefits outweigh the risks. However, in such cases, the newborn may be at risk for mild signs and symptoms of DS post-delivery. Therefore, the infant should remain in hospital for a longer period of time than the usual 48 hours or less, to enable close monitoring.[33-35] The incidence of neonatal serotonin DS associated with antidepressant exposure varies in the literature, but is thought to range from between 22–30%.[34] There is debate in the literature as to the risk factors for developing neonatal serotonin DS. Some believe that the chance of developing DS may be related to the following independent factors: the drug's propensity to cross the placenta, the half-life of the agent and the dose that the neonate was exposed to during pregnancy.[34]

Antidepressant DS symptoms experienced in such newborns include tremor, jitteriness, irritability, increased tone, increased respiratory rate, diarrhea, sleep problems and poor feeding.[33-37] Such symptoms typically appear within the first 24–48 hours of life.[33,34] Of interest, the severity of symptoms reported in the literature seems to vary and no clear correlation to maternal dose with various agents has been found. It has been suggested that antidepressants metabolized through cytochrome P450 (CYP450) may influence drug concentrations in the body and the resultant degree of DS observed. Neonatal CYP450 enzymes are immature and, as such, neonates should be considered slow metabolizers (for example, their CYP2D6 enzyme capacity is only 5% of that of an adult at birth and only increases to 20% by 1 month of age). In addition, the presence of any maternal genetic polymorphism in the CYP enzyme (e.g., 2D6 or 3A4) responsible for the drug's metabolism may lead to higher amounts of drug transferred to the fetus, resulting in a greater degree of DS symptoms in the newborn.[35]

Whether treatment for DS in newborns is required or should be provided has not been sufficiently studied. If no treatment is provided, symptoms usually disappear after two to four weeks of life.[38] If treatment is started, the most common approach is to use phenobarbital for symptomatic

management.[33] Theoretically, although not done in practice due to lack of evidence, one could expose the neonate to a serotonergic agent and taper it gradually in a manner similar to how morphine is weaned when it is being given for neonatal opioid withdrawal. However, this approach has not yet been studied.[33]

Breastfeeding while the mother continues on antidepressant therapy may theoretically help reduce symptoms of neonatal serotonin DS depending on how much of the drug enters the breastmilk, but its role as either a protective or risk factor is controversial.[34] Most antidepressants have a high rate of placental passage and relatively low rate of breastmilk excretion, making the hypothesis that breastfeeding may be protective questionable. The results of one recent study showed that neonates were still at significant risk of DS despite being breastfed.[34] On the other hand, another recent study found that breastfeeding was protective and mitigated serotonin DS symptoms in neonates exposed to venlafaxine in the third trimester.[35]

Treatment of DS

When signs and symptoms can be attributed to DS, they will resolve simply and quickly after drug reinstitution, even at markedly reduced doses.[1,39] After temporary reinstatement of the medication, the drug can be slowly tapered to prevent discontinuation symptoms.[18] However, there are no clear, validated tapering methods.[16] Depending on the drug, discontinuation syndromes may last for days to a period of months (e.g., with paroxetine). In rare and more serious cases involving psychosis, catatonia or severe cognitive impairment, immediate consultation with a psychiatrist or interventions through the local emergency room may be warranted.[16]

The pharmacist's role

Community pharmacists are well-situated to identify the early signs and symptoms of DS and help patients before negative outcomes occur. The acronym FINISH is a helpful tool to aid the community pharmacist in identifying DS in patients:[16,19]

- Fever/ Flu-like symptoms
- Insomnia
- Nausea
- Irritability
- Sensory changes
- Headache

Pharmacists can also be alert for late refills among mental health patients or patients describing adverse effects such fever, irritability, nausea, insomnia or sensory changes. For example, patients may be searching for an herbal or OTC agent to help with these iatrogenic- or discontinuation-mediated ailments. Including a question about other medications being taken is already a component of the standard questions asked by pharmacists when making OTC recommendations. Inquiring whether doses of mental health drugs have recently been missed is an easy and valuable way to reinforce adherence and assist in determining whether DS is in fact the cause for the OTC query. Late refills are the easiest early warning signal for a community pharmacist that a patient may be nonadherent.

Pharmacists should also proactively prevent DS by educating patients about the possibility of developing DS if they abruptly stop their mental health medications.[18] Patient education about DS is important as it can help to dispel a common misconception that mental health medication are 'addictive' because of the withdrawal symptoms that occur when they are stopped.[18]

Conclusion

Given the fact that, within the lifetime of the general population, up to 25% may have depression, one to two per cent may have schizophrenia and five to seven per cent may have bipolar disorder, community pharmacists are guaranteed to be involved with mental healthcare patients.[12] As such, they need to be aware of the main drugs that can produce DS when abruptly stopped and the main factors precipitating DS. These include higher doses, usage for a prolonged duration of time or history of substance abuse, or drugs that have no active metabolites. Additionally, by recognizing characteristic symptoms, educating physicians and patients to avoid abrupt discontinuation and providing adequate patient counselling and follow-up, pharmacists can play an active role in diminishing the occurrence of DS.

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