Review

Relapse vs. Withdrawal:
The Principles of Discontinuation Syndrome

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Understanding discontinuation syndrome (DS) and becoming familiar with the medications that cause it are important issues in the treatment of patients with mental health conditions. The purpose of this article is to enhance awareness among physicians of the potential for mental health patients to experience DS. One of the major challenges in recognizing DS, resulting from psychoactive medication, is that its symptoms often mimic the initial condition being treated. (Although DS is also seen with other drugs, including ß-blockers [*e.g.*, propranolol] and narcotics/opiates, these will not be addressed herein). Even with commonly prescribed medications, such as antidepressants, only 72% of psychiatrists and 30% of GPs were aware that patients may experience DS.[1]

What is DS?

DS is a condition where the patient experiences adverse effects that result from an abrupt discontinuation of a medication. Symptoms of DS generally begin to appear within the first 24 hours to 48 hours after drug discontinuation or dose reduction and last for up to seven days to 14 days, depending on the medication.[2] Also, some adverse effects from discontinuation may persist for several months, as seen with paroxetine.

Symptoms of DS are distinct from relapse of the underlying disease and will resolve after drug reinstitution, but as alluded to, they often mimic or appear to be a relapse of the initial mental health condition.[2-3] It becomes an important issue for physicians, since patients receiving mental health-care inherently lapse in treatment compliance, due to either cost, adverse effects or stigma and also, in medical situations where there is a decision to stop medication (*e.g.*, pre- and post-operatively).[4]

Medications causing DS

There are four classes of drugs implicated in DS that we will cover (Table 1):

1) Tricyclic antidepressants (TCAs)
2) Selective serotonin reuptake inhibitors (SSRIs)/ serotonin-norepinephrine reuptake inhibitors (SNRIs)
3) Antipsychotics (*e.g.*, olanzapine, quetiapine, risperidone and clozapine)
4) Benzodiazepines (BZDs)

If we look at the numbers, up to 30% of the population may need one of these four classes of drugs, for depression, schizophrenia or bipolar disorder, in their lifetime.

Etiology

Physiological dependence on these medications is a normal consequence of pharmacological receptor site activity.[2,5-7] Receptors that may be involved with the TCA agents (*e.g.*, imipramine) can be be explained by adrenergic overdrive or cholinergic overdrive (Table 1).

Antidepressant DS may occur with TCAs, SSRIs and monoamine oxidase inhibitors (MAOIs). Symptoms usually start within a few days of treatment cessation, at most; they occur more rarely when tapering down a dosage. Distinguishing antidepressant DS from

Table 1

Comparison of medication causing discontinuation syndrome (DS)

Drug class	Proposed causation mechanisms	Drugs with reported incidents of DS	Physical effects	Psychological effects	Risk factors
• Tricyclic antidepressants (TCAs)[2]	• Adrenergic overdrive - TCAs inhibit norepinephrine (NE) uptake and increased synaptic NE concentrations - α–2 receptor stimulation occurs via negative feedback resulting in decreased adrenergic firing - Prolonged TCA use causes blunting of this loop and when TCA is stopped, the negative feedback loop results in inhibited adrenergic firing (adrenergic excess symptoms) • Cholinergic overdrive - TCA binds to muscarinic receptors centrally and peripherally - Persistent cholinergic blockade leads to muscarinic receptor up-regulation - When TCA is stopped, there is temporary cholinergic hyperactivity	• Imipramine	• Lethargy • Headache • Tremor • Sweating • Anorexia • Insomnia • Nausea • Vomiting • Diarrhea	• Irritability • Anxiety/ agitation • Low mood • Excessive dreaming • Nightmares • Paradoxical activation	Risk factors may be directly related to higher doses, active metabolites, or usage for prolonged duration of time, as well as a past history of substance abuse
• Selective serotonin reuptake inhibitors (SSRIs) • Serotonin-norepinephrine reuptake inhibitors (SNRIs) • Noradrenergic and specific serotonergic antidepressants (NaSSAs)[2,9-11]	• Persistent increased concentration of serotonin in synapse • Desensitization of the postsynaptic 5-HT receptor via down-regulation • When the agents are stopped, there is a temporary deficiency of serotonin in the synapse	• Examples of agents in classes: - Paroxetine (SSRI) - Venlafaxine (SNRI) - Mirtazapine (NaSSA)	• Flu-like symptoms • Dizziness • Fatigue • Headache • Insomnia	• Anxiety • Agitation • Rebound panic disorder • Insomnia	• SSRIs with short half-life • Antidepressant therapy lasting > 4 weeks • Patients with a history of treatment, emergent anxiety, DS and non-adherence
• Antipsychotics[2,12-18]	• Most atypical agents have some serotonin-dopaminergic antagonism • Clozapine is the most likely to produce a DS • Weak dopamine D2 antagonist and potent serotonin (5HT2) antagonism • May have antagonism at the α-adrenergic, histaminergic and cholinergic receptors • There is a rebound from these receptors when these agents are discontinued	• Olanzapine	• Cholinergic/ serotenergic syndrome	• Super-sensitivity psychosis	Risk factors may be directly related to higher doses, active metabolites or usage for prolonged duration of time, as well as a past history of substance abuse
		• Risperidone	• Tics • Movement disorders • Withdrawal • Emergent dyskinesias		
		• Quetiapine	• Nausea • Emesis • Dizziness • Diaphoresis • Orthostasis • Tachycardia • Nervousness	• Nervousness	
		• Clozapine	• Extra-pyramidal symptoms • Nausea • Headache • Diarrhea • Restlessness	• Exacerbation of psychosis • Delirium • Catatonia • Agitation • Confusion • Diaphoresis	
Benzodiazepines (BZDs)[2,13-14]	• Modulate neurotransmitter activity of γ-aminobutyric acid (GABA) • Agents differ in pharmacokinetic properties and have varying half lives • Interact with binding sites on GABA receptor complex and increase receptor affinity for GABA • When stopped, decrease GABA binding sites/inhibitory effects and increase glutamate • Chronic use leads to adaptive changes (GABA receptor down-regulation and increased glutamate)	• Intermediate-acting: - Alprazolam - Lorazepam - Oxazepam • Short-acting: - Triazolam	• Insomnia • Tachycardia • Mild systolic hypertension • Anxiety • Nausea • Nervousness • Sweating • Panic attacks • Tremor • Seizures	• Increased risk of agitation • Decreased sleep	• Pharmacokinetics (short half-life) • Pharmacodynamics (high receptor affinity) • Dose • Duration of use • Pre-existing history of dependence

the underlying depression is important. DS symptoms usually present within one day to three days, whereas depressive symptoms usually only present two weeks to three weeks after antidepressant medication is stopped. DS usually subsides in a few days, especially if antidepressant treatment is re-started. Up to 30% of patients who stop SSRI treatment will experience DS.

Distinguishing antidepressant DS from the underlying depression is important. DS symptoms usually present within one day to three days, whereas depressive symptoms usually only present two weeks to three weeks after medication is stopped.

The proposed mechanisms in SSRI-related DS include an increased concentration of serotonin in the synapse, which results in a desensitization of the postsynaptic serotonin receptor by down-regulation. When the agents are discontinued, there is a temporary deficiency of serotonin in the synapse, which leads to the physical symptoms.

DS was first identified in the antipsychotic drug chlorpromazine in the late 1950's, when it was being tested as an anti-TB agent. The DS occurred in five out of 17 subjects. Most atypical antipsychotic agents have some serotonin-dopamergic antagonism and now there are case reports for all of the atypical agents. The proposed mechanism of action is that there is weak dopamine D2 antagonism and potent serotoninergic (5HT2) antagonism. Also, antipsychotic drugs inherently have antagonistic effects at the α-adrenergic, histaminergic and chlolinergic receptors, with the ratio depending on the individual agent. Thus, we see a rebound from these receptors when the agent is stopped. This also explains why the atypical agents have a very specific DS for each different agent.

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. When the benzodiazepine is stopped, there is decreased GABA binding sites/ inhibitory effects, as well as increased glutamate, which yield the 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.

Conclusions and impact to practice

Given the fact that, within the lifetime of the general population, up to 25% may have depression, 1% to 2% may have schizophrenia and 5% to 7% may have bipolar disorder, physicians involved in mental health-care need to be aware of the main factors precipitating DS. These include risk factors that may be directly related to higher doses, usage for prolonged duration of time or past history of substance abuse,[8] considering the psychological "need" to continue with a medication. Additionally, by recognizing characteristic symptoms,

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avoiding abrupt discontinuation and providing adequate patient counselling and followup, physicians can play an active role in diminishing the occurrence of DS.

Clinically and for teaching, a helpful tool to aid the GP/FP identify DS in patients is the the acronym FINISH:

- Fever
- Insomnia
- Nausea
- Irritability
- Sensory Changes
- Headache

We must be aware that if a patient presents with any of the signs and symptoms listed above, it may be the result of medication discontinuation. In general, the signs and symptoms of DS occur before the relapse of the axis-1 disorder, since the condition manifests within hours of drug discontinuation. There are numerous variables affecting the speed and degree of symptom onset. Patient-specific factors to consider include:

- diet,
- hydration and
- compliance.

There are also medication-specific variables, which include:

- concurrent medications that may affect metabolism,
- half-life of the medication and
- active metabolites.

Other factors may include:

- a patient's dependence lability (psychological vs. physical withdrawal syndromes) and
- duration of therapy with the agent. Dx

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