Opioid dose reduction or transition to another opioid therapy often results in uncomfortable signs and symptoms of withdrawal. The severity of these symptoms can fluctuate among patients, even among those with similar body mass index, gender, and dosage. Several theories have been proposed regarding the contribution of noradrenergic pathways in the expression of opioid withdrawal.\(^1\) In the central nervous system, the major clustering of norepinephrine-producing neurons is in the locus coeruleus (LC). Levels of norepinephrine and its metabolites are altered during opioid dependence, resulting in somatic opioid withdrawal symptoms.\(^1\) Other studies have suggested that alterations in the density and sensitivity of alpha and beta adrenergic receptors plays a role.\(^1\) Still, others suggest that a mesolimbic dopaminergic system contributes to opioid withdrawal symptomatology.\(^2\)

In October, *Practical Pain Management* featured an article by Hymes et al on the use of percutaneous electrical neurostimulation to treat withdrawal symptoms.\(^3\) In this article, the authors examine pharmaceutical ways to attenuate withdrawal symptoms. By taking advantage of alpha- and beta-agonists and antagonist, clinicians can provide faster tapers and less withdrawal symptoms—without adding a new medication to patients polytherapy.

**Symptoms of Opioid Withdrawal**

Opioid receptor activation is mediated by 3 different opioid receptors: delta, kappa, and mu. Symptoms of opioid withdrawal may begin 8 to 10 hours after the last dose, depending on the half-life and volume of distribution of the opioid (Table 1). The dosage form and route of administration
can influence a drug’s pharmacokinetic parameters and the onset of withdrawal following cessation of the drug.

The majority of opioid withdrawal symptoms reflect increased activity of the autonomic nervous system (ANS). While hyperactivity of noradrenergic neurons within the LC has been associated with somatic symptoms of opioid withdrawal, it is also noteworthy that the LC is involved with various neurophysiologic functions, including learning processes and the emotions of anxiety and fear. For these reasons, it is thought that excessive activation of the LC noradrenergic neurons not only induces somatic symptoms of opioid withdrawal but also causes the cognitive and emotional problems associated with withdrawal.

The initial phase of withdrawal includes acute symptoms such as lacrimation, rhinorrhea, yawning, and sweating that may last 7 to 10 days as well as symptoms that occur later, such as restless sleep, weakness, chills, nausea and vomiting, muscle aches, and involuntary movements. The secondary phase of withdrawal includes symptoms such as hypotension, bradycardia, hypothermia, mydriasis, and decreased responsiveness of the respiratory system to carbon monoxide. The secondary phase can last anywhere from 26 to 30 weeks. The Clinical Opioid Withdrawal Scale (COWS) is a tool used by clinicians to assess the degree of withdrawal a patient is experiencing based on current symptoms. The COWS reflects the assessment of 11 symptoms: vital signs (pulse), a brief physical exam (pupil size, sweating, restlessness, runny nose or eye tearing, achiness, GI distress, tremor, yawning, gooseflesh skin) and mental status (irritability or anxiety).

These symptoms are then converted into a numeric score based on their severity. These numbers are totaled to form an overall score, from 0 (indicating no withdrawal symptoms) to 48 (the maximum degree of withdrawal

<table>
<thead>
<tr>
<th>Table 1: Opioid Half-Life and Volume of Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opioid</strong></td>
</tr>
<tr>
<td>Buprenorphine (buccal)</td>
</tr>
<tr>
<td>Buprenorphine (sublingual)</td>
</tr>
<tr>
<td>Buprenorphine (injection)</td>
</tr>
<tr>
<td>Buprenorphine (transdermal)</td>
</tr>
<tr>
<td>Cocaine (smoking)</td>
</tr>
<tr>
<td>Codeine</td>
</tr>
<tr>
<td>Fentanyl (buccal)</td>
</tr>
<tr>
<td>Fentanyl (injection)</td>
</tr>
<tr>
<td>Fentanyl (sublingual tablet)</td>
</tr>
<tr>
<td>Fentanyl (transdermal)</td>
</tr>
<tr>
<td>Heroin</td>
</tr>
<tr>
<td>Hydrocodone</td>
</tr>
<tr>
<td>Hydromorphone</td>
</tr>
<tr>
<td>Methadone*</td>
</tr>
<tr>
<td>Morphine (IR)</td>
</tr>
<tr>
<td>Oxycodone (IR)</td>
</tr>
<tr>
<td>Oxymorphone (IR)</td>
</tr>
<tr>
<td>Tramadol</td>
</tr>
</tbody>
</table>

* Large range in variable half-life due to polymorphisms.

h, hour; IR, immediate release.
Opioid Withdrawal: A New Look at Medication Options

PracticalPainManagement.com   |   November 2015

symptoms). These scores typically are used to determine whether buprenorphine induction is appropriate, with mild to moderate withdrawal symptoms being the ideal time to begin buprenorphine therapy.7

Treatment of Withdrawal

There are myriad agents that can be used to support clinicians in their treatment of patients experiencing opioid withdrawal. The following is a summary of agents that can attenuate withdrawal symptoms (Table 2).

Alpha-1 Antagonists

Administration of the alpha-1 antagonists phenotolamine,6 phenoxybenzamine (Dibenzyline, others),6 and prazosin (Minpress, others)7 can decrease the occurrence of somatic symptoms associated with opioid withdrawal.

Trazodone (Oleptro, others) is a triazolopyridine derivate that is used as an antidepressant.8 Trazodone acts as a 5-serotonin (HT)2 receptor antagonist at high doses and inhibits the reuptake of serotonin at the presynaptic membrane. Trazodone also weakly inhibits alpha-2 adrenergic receptors and strongly inhibits postsynaptic alpha-1 receptors. Due to its ability to inhibit alpha-1 adrenergic receptors, we postulate that it has a role in opioid withdrawal. Interestingly, trazodone has been shown to bind to opioid receptors as well, but only at high concentrations.8

When studied in mice, trazodone was found to induce potent mu-1 and mu-2 opioid receptor–mediated pain relief. Schreiber et al evaluated the effects of trazodone on opioid withdrawal symptoms in morphine-dependent mice who were receiving a high dose of naloxone.9 They evaluated the intensity of withdrawal symptoms using 3 different behavioral measurements: rearing, jumping, and grooming and found that adding trazodone to naloxone in morphine-dependent mice effectively decreased opioid-withdrawal intensity.9

Alpha-2 Agonists

Another agent that is commonly used to attenuate opioid withdrawal is clonidine (Catapres, Kapvay, others). The use of clonidine for opioid withdrawal originally was proposed by DeStefano et al.10 In addition, studies have revealed that clonidine plays a role in reducing the negative motivational aspects of opioid withdrawal.11

A recent review article by Gowing et al evaluated the evidence for alpha-2 adrenergic agonists in the management of opioid withdrawal symptoms in people who are physically dependent on opioids.12 The review evaluated 25 randomized control trials consisting of 1,668 opioid-dependent patients who were being treated with either clonidine, lofexidine, guanfacine (Tenex, Intuniv, others), or tizanidine (Zanaflex, others). Twelve studies compared alpha-adrenergic agonists with decreasing doses of methadone (Dolophine, Methadose, others), 5 studies compared alpha-2 agonists with placebo, 4 studies compared the study drug with drugs used for specific symptom control in withdrawal, and 5 studies compared different alpha-2 adrenergic agonists to each other. Treatment duration averaged 1 to 2 weeks (shortest duration was 3 days, and longest duration was 30 days).

The review showed no difference in opioid withdrawal symptoms between those receiving central alpha-2 adrenergic agonists and those treated with decreasing doses of methadone.12 The chance of completing treatment also was similar with alpha-2 adrenergic agonists and decreasing doses of methadone. However, the duration of treatment was longer with methadone. There were fewer adverse effects with methadone withdrawal signs and symptoms occurred earlier in patients taking alpha-adrenergic agonists. Of note, clonidine and lofexidine were more effective than placebo in managing withdrawal from heroin or methadone and were more likely to be associated with treatment completion than placebo. The studies conclude that alpha-2 adrenergic agonists may be an alternative in treating opioid withdrawal.12

Sos et al evaluated the effects of the alpha-2 adrenergic agonist tizanidine in patients suffering from opioid addiction.13 In this study, 26 intravenous heroin users were divided into 2 groups; each group had the usual detoxification treatment, but patients in the experimental group were given tizanidine 8 mg three times daily. A subjective scale was used to determine severity of withdrawal using 7 key withdrawal symptoms (sweating, nervousness, insomnia, tremor, diarrhea, muscle pain, and drug craving). The results of the study showed that tizanidine treatment decreased the intensity of withdrawal symptoms and may have potential benefit in treating opioid withdrawal.13

Although there are no studies to suggest that methyldopa is useful in the prevention of withdrawal, because it is a centrally acting alpha-2 agonist we could postulate that it would provide some benefit in this setting.12

Beta-1 Antagonists And Beta-2 Antagonists

Propranolol (Inderal, InnoPran XL, others) and atenolol (Tenormin, others) have been reported to reduce somatic signs of spontaneous opioid withdrawal and naloxone-precipitated opioid abstinence.14 It is theorized that beta blockers can have these effects because they block the noradrenergic hyperactivity associated with supersensitive beta-adrenergic receptors that result from adaptive changes induced by chronic opioid exposure.19-21 Somatic symptoms, including jumping and wet dog
<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha-1 Antagonists</strong></td>
<td>Phentolamine (Catapres, others)</td>
<td>Blocks alpha-1 receptors, thus inhibiting the release of NE during noradrenergic hyperactivity (which occurs as a result of opioid withdrawal)</td>
<td>Yes⁶</td>
</tr>
<tr>
<td></td>
<td>Phenoxybenzamine (Dibenzyline, others)</td>
<td></td>
<td>Yes⁶</td>
</tr>
<tr>
<td></td>
<td>Prazosin (Minpress, others)</td>
<td></td>
<td>Yes⁷</td>
</tr>
<tr>
<td></td>
<td>Trazodone (Oleptro, others)</td>
<td></td>
<td>Yes⁸,¹⁴</td>
</tr>
<tr>
<td><strong>Alpha-2 Agonists</strong></td>
<td>Clonidine (Catapres, Kapvay, others)</td>
<td>Stimulates central alpha-2 receptors that inhibit the release of NE during noradrenergic hyperactivity (which occurs as a result of opioid withdrawal)</td>
<td>Yes¹⁰</td>
</tr>
<tr>
<td></td>
<td>Lofexidine</td>
<td></td>
<td>Yes¹²</td>
</tr>
<tr>
<td></td>
<td>Guanfacine (Tenex, Intuniv, others)</td>
<td></td>
<td>Yes¹²</td>
</tr>
<tr>
<td></td>
<td>Tizanidine (Zanaflex, others)</td>
<td></td>
<td>Yes¹³</td>
</tr>
<tr>
<td></td>
<td>Methyldopa</td>
<td></td>
<td>No¹²</td>
</tr>
<tr>
<td><strong>Beta-Adrenergic Antagonists</strong></td>
<td>Propranolol (Inderal, InnoPran XL, others)</td>
<td>Blocks beta-1 and beta-2 receptors (which become supersensitive as a result of adaptive changes induced by chronic opioid exposure) that inhibit release of NE during noradrenergic hyperactivity</td>
<td>Yes¹⁴-¹⁶</td>
</tr>
<tr>
<td></td>
<td>Atenolol (Tenormin, others)</td>
<td></td>
<td>Yes¹⁴-¹⁶</td>
</tr>
<tr>
<td></td>
<td>Metoprolol (Lopressor, Toprol XL, others)</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Nadolol (Corgard, others)</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Carvedilol (Coreg, others)</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Labetalol</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td><strong>NMDA Receptor Antagonists</strong></td>
<td>Dextromethamphetamine</td>
<td>Blocks NMDA receptors that may have a role in increasing the release of beta endorphins, thus attenuating withdrawal symptoms</td>
<td>Yes³⁰</td>
</tr>
<tr>
<td></td>
<td>Ketamine (Ketalar, others)</td>
<td></td>
<td>Yes²⁰</td>
</tr>
<tr>
<td></td>
<td>Memantine (Namenda, others)</td>
<td></td>
<td>Yes²¹</td>
</tr>
<tr>
<td></td>
<td>Amantadine</td>
<td></td>
<td>Yes²²</td>
</tr>
<tr>
<td></td>
<td>Dextromethorphan</td>
<td></td>
<td>Yes²³-²⁵</td>
</tr>
<tr>
<td></td>
<td>Orphenadrine (Norflex, others)</td>
<td></td>
<td>No³⁰</td>
</tr>
<tr>
<td><strong>Serotonergic and Norepinephrine Reuptake Inhibitors</strong></td>
<td>Venlafaxine (Effexor, others)</td>
<td>Blocks the reuptake of serotonin, which may have a role in decreasing the release of NE centrally, but further studies are warranted to determine the role of serotonin in opioid withdrawal.</td>
<td>Yes²⁷-²⁹</td>
</tr>
<tr>
<td></td>
<td>Mirtazapine (Remeron, others)</td>
<td>Mirtazapine increases release of dopamine by inhibiting alpha-2 adrenoceptors in the cerebral cortex and by blocking 5-HTc2 receptors, which generally block prefrontal cortex release of DA. Mirtazapine increases the release of dopamine, which may have a role in reducing acute withdrawal symptoms and inhibiting opioid cravings</td>
<td>Yes³⁰</td>
</tr>
</tbody>
</table>
shakes, were both blocked by beta-1 antagonists, whereas beta-2 antagonists have been shown to suppress the incidence of wet dog shakes only.\textsuperscript{14}

Propranolol and atenolol have been shown to reduce withdrawal-induced anxiety in animals.\textsuperscript{15,16} Addicts have reported that anxiety associated with opioid withdrawal often returns when they are in an environment that is associated with drug use. Harris and Aston-Jones conducted a study to investigate whether propranolol and atenolol reduced somatic symptoms and whether the medications reduced place aversion in opioid-abstinent rats.\textsuperscript{15,16} The most common somatic symptoms included wet dog shakes, teeth chatter, writhing, and vocalization upon touch. Place aversion was tested by injecting the rats with naloxone in one area of the cage and then observing whether the rats avoided that area. The investigators found that beta-adrenergic antagonists reduced somatic symptoms and alleviated withdrawal-induced anxiety.

Beta receptors have a role in promoting consolidation and retrieval of memory; thus, in theory, blocking this pathway with a beta-adrenergic antagonist would prevent such memories from forming.\textsuperscript{17} Animal studies have suggested that propranolol can disrupt memory reconsolidation that previously had been associated with rewarding medications such as morphine.\textsuperscript{17,19} Such results imply that by preventing the memory of the rewarding effects of the medication, propranolol could be effective for preventing relapse in addicts.

Although a prior study by Robinson et al showed that propranolol disrupted memory reconsolidation associated with morphine,\textsuperscript{18} when they tested this theory in rats, they found that in a setting of exposure to high doses of morphine, propranolol was not able to disrupt memory reconsolidation.\textsuperscript{19} This study indicates that chronic exposure to morphine markedly alters the effects of propranolol as a reconsolidation blocking treatment.\textsuperscript{19}

### NMDA Receptor Antagonists

Some evidence suggests that another mechanism responsible for tolerance to and withdrawal from opioids involves activation of N-methyl-D-aspartase (NMDA) receptors. Thus, it has been theorized that NMDA antagonists may decrease withdrawal symptoms.\textsuperscript{20}

Bisaga et al demonstrated that the NMDA-receptor antagonist memantine (Namenda, others) decreased naloxone-induced symptoms of withdrawal in heroin-addicted patients.\textsuperscript{21} Amantadine, another NMDA antagonist with dopaminergic, adrenergic, and serotonergic properties (MAO-A inhibition), also has been theorized to have efficacy in the treatment of opioid-withdrawal symptoms. Amiri et al found that amantadine plus clonidine was superior to clonidine alone in controlling opioid-withdrawal symptoms for a duration of 3 days in a study involving 69 patients.\textsuperscript{22} The mechanism of action may be due to NMDA-receptor inhibition and MAO inhibition, which cause an increase in beta-endorphins. Amiri et al showed a trend for increased withdrawal symptoms on day 3, thus, studies done with amantadine for a longer duration are warranted.

The antitussive dextromethorphan is another agent that, theoretically, can provide benefit for patients

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
\textbf{Dopaminergic Agonists} & \\
\hline
Levodopa & Increases the release of dopamine, which may have a role in reducing acute withdrawal symptoms and inhibiting opioid cravings. L-dopa increased aggression during opioid withdrawal, while quinpirole decreased aggression. & No\textsuperscript{33} \\
\hline
Quinpirole & Levels of dopamine increase acutely during opioid administration and then decreases after opioid withdrawal; thus, it has been hypothesized that a decrease in dopaminergic neurotransmission may be associated with some of the unpleasant subjective symptoms associated with drug withdrawal. & Yes\textsuperscript{16} \\
SKF82958 & & Yes\textsuperscript{16} \\
\hline
\textbf{Dopaminergic Antagonists} & \\
Haloperidol (Haldol, others) & Unknown & Yes\textsuperscript{17} \\
Droperidol & & Yes\textsuperscript{16} \\
\hline
\textbf{Miscellaneous} & \\
Bupropion (Aplenzin, Buproban, others) & Inhibits reuptake of dopamine, and, thus, may have a role in reducing acute withdrawal symptoms and inhibiting opioid cravings & Yes\textsuperscript{16} \\
\hline
\end{tabular}
\caption{Summary of Agents That Attenuate Opioid Withdrawal (Continued)}
\end{table}

\textit{DA}, dopamine; \textit{NE}, norepinephrine; \textit{NMDA}, N-methyl-D-aspartase
experiencing opioid withdrawal, based on its ability to inhibit NMDA receptors. Dextromethorphan is metabolized to dextrophan, the pharmacologic activity of which is primarily at the NMDA receptor. (Dextromethorphan binds to NMDA binding sites with a 10-fold lower affinity than dextrophan.)

In a randomized clinical trial involving 48 heroin addicts, dextromethorphan showed benefit in attenuating withdrawal symptoms. Dextromethorphan combined with diazepam (Valium, others) had greater efficacy compared with diazepam and chlorpromazine combined.

However, Rosen et al found that oral dextromethorphan (60 mg, 120 mg, or 240 mg) did not attenuate withdrawal symptoms in 11 subjects who experienced naloxone-precipitated withdrawal after being stabilized on oral methadone 25 mg per day. Subjects received challenges with 0.4 mg of intramuscular naloxone on 3 different days and were randomized to receive either dextromethorphan or placebo. Patients taking dextromethorphan showed no difference in withdrawal symptoms compared with patients taking placebo.

Bisaga et al showed beneficial data for withdrawal with dextromethorphan in 6 male patients who were daily heroin users. The patients in this trial were hospitalized during the study, and all received 75 mg of dextromethorphan 5 times per day (no other medications were given besides hydroxyzine [Vistaril, others], acetaminophen [Tylenol, others], and ibuprofen [Advil, Motrin, others]). Two patients dropped out of the study, but the 4 patients who completed the study reported a subjective difference from previous detoxification with methadone; they all had a rapid and thorough decrease in signs, symptoms, and craving associated with opioids by the fourth day of treatment. Patients received treatment for an average of 6 days and were discharged after being free from medication for 1 day. Results of this trial indicate that dextromethorphan may be an inpatient treatment option in patients suffering from opioid withdrawal.

Of note, efficacy in treating opioid withdrawal symptoms can be expected from dextromethorphan due to its NMDA-antagonist properties, not due to its effects as an opioid agonist. Dextromethorphan’s binding affinity to mu opioid receptors is 6,000 times less than that of morphine; thus, we would not see much efficacy to diminish withdrawal symptoms due to its mu opioid–receptor activity.

Orphenadrine (Norflex, others), a commonly used muscle relaxant, is an anticholinergic medication with NMDA-antagonist properties. Theoretically, orphenadrine can be used for opioid withdrawal due to its ability to inhibit NMDA receptors. Although there have been no studies conducted to substantiate the role of orphenadrine in opioid withdrawal, anecdotal reports have noted benefit from its use to mitigate such symptoms.

Serotonergic and Norepinephrine Reuptake Inhibitors
Venlafaxine (Effexor, others) is a novel antidepressant that blocks reuptake of norepinephrine and serotonin. It has been postulated to mitigate opioid withdrawal due to its serotonin reuptake-blocking properties. In a study by Lu et al, rats treated with chronic morphine were pretreated with venlafaxine or not given anything before administration of naloxone. Pretreatment significantly attenuated the rats’ symptoms of morphine withdrawal, including jumping, writhing, shaking, exploring, lacrimation, piloerection, irritability, and diarrhea. Venlafaxine also attenuated morphine-induced reacquisition of conditioned place preference in these rats. However, because there is limited evidence to suggest that the serotonergic system is involved in opioid withdrawal, more studies are warranted to determine if the serotonergic properties of venlafaxine contribute to the attenuation of withdrawal symptoms.

Although there is limited evidence for the role of serotonergic neurotransmission in opioid dependence and withdrawal, the selective serotonin reuptake inhibitors (SSRI) fluvoxamine and sertraline (Zoloft, others) have been shown to decrease the intensity of physical signs of naloxone-induced opioid withdrawal. In an experiment conducted by Gray, naloxone increased norepinephrine levels in the hippocampus of morphine-dependent rats 20 minutes after administration, and withdrawal-induced physical behaviors were apparent 5 minutes after injection. Study animals were given either fluvoxamine or sertraline, either acutely (after discontinuation of 8 days of therapy with morphine and right before naloxone administration) or chronically (after daily morphine doses for 8 days). Chronic administration of both SSRIs reduced the severity of naloxone-precipitated opioid withdrawal syndrome and prevented naloxone-precipitated increases in hippocampal levels of norepinephrine.

However, acute administration did not prevent naloxone-precipitated increases in norepinephrine in the hippocampus. Acute administration of SSRIs only reduced the intensity of physical symptoms of naloxone-precipitated opioid withdrawal. The principal finding of the study was that fluvoxamine given once daily following morphine prevented an increase in norepinephrine levels and the physical behaviors of opioid withdrawal, and reduced levels of norepinephrine in the hippocampus of morphine-dependent rats.
Theories about the ability of SSRIs to ameliorate symptoms of opioid withdrawal suggest that increased serotonin in the synaptic cleft can increase the inhibitory tone of the LC, causing lower levels of noradrenergic activity within the LC. Another hypothesis suggests that SSRIs may be involved in increasing endogenous opioid levels, which can cause a decrease in nor-epinephrine levels.

Mirtazapine (Remeron, others) is an antidepressant with noradrenergic and serotonergic properties. More specifically, mirtazapine is a potent pre-synaptic alpha-2 receptor antagonist, 5-HT\textsubscript{1}, receptor agonist, and 5-HT\textsubscript{2} and 5-HT\textsubscript{3} antagonist. A study conducted by Kang et al tested the acute and chronic effects of mirtazapine on rats that were given morphine for 10 days. The acute effects of mirtazapine were observed by administering mirtazapine 15 minutes before naloxone. The chronic effects of mirtazapine were tested by administering mirtazapine 15 minutes before daily doses of morphine. The experiment recorded 8 behaviors (wet dog shakes, digging, teeth chattering, rearing, grooming, chewing, scratching, and escape attendance) over a period of 30 minutes.

Overall, the results of the study showed that chronic mirtazapine can reduce the severity of withdrawal symptoms, inhibit the craving for morphine, and may decrease the rewarding effects of morphine in rats. Also, mirtazapine caused pronounced elevation in dopamine levels. Kang et al proposed that mirtazapine increases levels of dopamine by inhibiting alpha-2 adrenergic receptors in the cerebral cortex and by blocking 5-HT\textsubscript{2} receptors that generally block prefrontal cortex release of dopamine. The rise in dopamine is inhibiting opioid craving in rats. More studies are warranted to explore the role of mirtazapine in the treatment of opioid dependence and withdrawal in humans.

**Dopaminergic Agonists And Antagonists**

There are contradictory data on the role of dopamine agonists and antagonists in morphine withdrawal. For example, amphetamine, apomorphine, and levodopa have been shown to increase aggression in rats undergoing morphine withdrawal but quinpirole decreases aggression associated with morphine withdrawal. Furthermore, Harris and Aston-Jones found that activation of D\textsubscript{2} dopaminergic receptors within the NAc prevented some of the somatic symptoms of opioid withdrawal.

Radhke and Gewirtz examined the effects of dopamine agonists on withdrawal-induced anxiety following spontaneous withdrawal from acute morphine exposure. They examined the effects of intracerebrally infused dopamine-receptor agonists on the potentiation of acoustic startle reflex, which likely represent the anxiety-like component of withdrawal. The experiments used 2 dopamine receptor agonists, SKF82958 (D\textsubscript{1} receptor agonist) and quinpirole (D\textsubscript{2} receptor agonist), and randomly injected either medication during morphine withdrawal in rats. The study found that activation of D\textsubscript{1} and D\textsubscript{2} like receptors attenuated opioid withdrawal–induced anxiety and, thus, support the theory that diminishing activity at both D\textsubscript{1} and D\textsubscript{2} like receptors have a role in the expression of opioid withdrawal.

From a pharmacologic perspective, since opioid withdrawal is associated with a reduction in the release of dopamine along the mesolimbic pathway, dopamine agonists have shown some benefit for opioid withdrawal. Counterintuitive to this is the fact that some dopamine antagonists, in particular the butyrophenones haloperidol (Haldol, others) and droperidol, have some benefit in withdrawal too. Both butyrophenone antipsychotics block postsynaptic mesolimbic dopaminergic D\textsubscript{2} receptors in the brain and reduce dopaminergic neurotransmission in the 4 dopaminergic pathways.

Haloperidol has been shown to markedly decrease morphine withdrawal-induced aggression. Rodriguez-Arias et al revealed that aggressive behavior in rats decreased when they were administered haloperidol during either naloxone-precipitated or spontaneous withdrawal. This study suggested that anti-aggressive effects of haloperidol were more pronounced in naloxone-precipitated withdrawal than in spontaneous withdrawal.

Sivolap and Savenkov examined 197 patients who were treated with haloperidol and droperidol following opioid withdrawal. They found that withdrawal-induced psychosis was relieved with droperidol and haloperidol, and these 2 agents were especially helpful in the acute phase of withdrawal. Although the exact mechanism through which these agents attenuate symptoms of withdrawal are unclear, it is evident that these agents have some benefit in opioid withdrawal.

**Miscellaneous**

Bupropion (Aplenzin, Buproban, others), a norepinephrine and dopamine reuptake inhibitor, has shown some benefit in opioid withdrawal. Joshi et al studied the effects of bupropion on morphine tolerance and dependence in mice. They gave mice bupropion therapy (2 or 5 mg/d) with morphine for 10 days. When naloxone was administered, the mice treated with bupropion had less withdrawal-induced jumps. Furthermore, acute administration of bupropion on day 10 decreased the incidence of naloxone-precipitated withdrawal jumps without causing...
tolerance to the analgesic effect. The results of this study suggest that bupropion may have potential in opioid withdrawal.

Although the exact mechanism for bupropion’s efficacy in opioid withdrawal is unknown, its ability to decrease reuptake of dopamine may contribute to attenuation of withdrawal symptoms.

**Summary**

A person’s ability to tolerate a rapid opioid taper and substantial dose reductions when converting to other opioids can, in large part, depend on their concomitant medical therapies. These therapies, which may have been prescribed for any number of disorders, can directly or indirectly affect the symptomatic and parasympathetic nervous systems. All of these factors should be carefully considered when tapering or switching opioids.

**Authors’ Bios:** At the time of this writing, Dr. Nabeela Ahmed was a PharmD Candidate, 2015 at the Albany College of Pharmacy and Health Sciences. She is currently a PGY-1 Pharmacy Resident at New York University Langone Medical Center in New York City.

At the time of this writing, Dr. Randall Horlacher was a PharmD Candidate, 2015 at the University at Buffalo School of Pharmacy and Pharmaceutical Sciences. He is currently in community practice in Harrisburg, Pennsylvania.

Jeffrey Fudin, BS, PharmD, DAAPM, FCCP, FASHP, is Adjunct Associate Professor of Pharmacy Practice & Pain Management, Western New England University College of Pharmacy, in Springfield, Massachusetts. He also is Adjunct Assistant Professor of Pharmacy Practice, University of Connecticut School of Pharmacy, in Storrs, Connecticut, and Clinical Pharmacy Specialist and Director, PGY2 Pain & Palliative Care Pharmacy Residency at the Stratton VA Medical Center, in Albany, New York.

Dr. Fudin graduated from the Albany College of Pharmacy & Health Sciences with his Bachelors Degree and his PharmD. He was awarded and completed an American Cancer Society Sponsored Fellowship in Oncology/Hematology at SUNY/Upstate Medical Center shortly after his undergraduate work.

Dr. Fudin practices as a Clinical Pharmacy Specialist and Director, PGY-2 Pharmacy Pain Residency Programs at the Stratton Veterans Administration Medical Center. He is an Adjunct Associate Professor of Pharmacy Practice at Western New England University College of Pharmacy; Adjunct Assistant Professor of Pharmacy Practice at Albany College of Pharmacy; Adjunct Assistant Professor of Pharmacy Practice at the University of Connecticut School of Pharmacy; and has several other academic affiliations including and the University at Buffalo School of Pharmacy and Pharmaceutical Sciences. He has been an Instructor of Pharmacology at SAGE Graduate School of Nursing for several years. He is a Clinical Pharmacy Consultant to HomeMed Associates, an innovative home-based academic patient care service dedicated to treating medically complex patients in their homes.

He is a Diplomate of the American Academy of Pain Management, a Fellow of the American College of Clinical Pharmacy, and a member of several other professional organizations. Dr. Fudin is a Section Editor for Pain Medicine, the official journal of AAPM. He is Founder/Chairman of Professionals for Rational Opioid Monitoring & Pharmacotherapy (PROMPT), a group that advocates in favor of safe opioid prescribing by encouraging clinician education, proactive risk stratification, and appropriate therapeutic monitoring.

Drs. Fudin, Ahmed, and Horlacher disclosed that their involvement with this article was not prepared as part of their official government duties.

Practical Pain Management readers will recognize Dr. Fudin as one of the codevelopers of the PPM Opioid Calculator.

**References**

Opioid Withdrawal: A New Look at Medication Options


