



Dextromethorphan abuse: Clinical effects and management

Frank Romanelli and Kelly M. Smith

Abstract

Objective: To describe the epidemiology, patient presentation, and clinical management associated with dextromethorphan (DM) abuse.

Data sources: PubMed/Medline search using terms *dextromethorphan* and *abuse* through July 2008, bibliographies of selected publications, epidemiology tracking databases.

Study selection: By the authors.

Data extraction: English language–published review articles, clinical trials, and case reports that described the epidemiologic and toxicologic profile of DM were included.

Data synthesis: DM is a relatively inexpensive and easily accessible over-the-counter (OTC) medication intended for use as an antitussive. Increasingly, illicit use of the drug has been reported. At clinical doses, the drug produces few adverse effects. **However, when abused in large quantities (>2 mg/kg), the drug has been associated with a dissociative effect similar to those described by ketamine and phencyclidine abusers.** Massive ingestions of the drug may be associated with untoward effects, including tachycardia, hypertension, and respiratory depression. Overdose symptoms may also be associated with coformulated products such as antihistamines and sympathomimetic amines. Management is primarily supportive. Naloxone has been used to manage DM toxicity but with conflicting reports of effectiveness.

Conclusion: Recent reports indicate that DM is often abused by individuals seeking its dissociative effects. Clinicians should be aware of the abuse potential of DM. Pharmacists might be particularly cognizant of the risks involved with DM abuse as they control OTC access to the drug.

Keywords: Dextromethorphan, drug abuse, drug–drug interactions.

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Learning objectives

At the conclusion of this program, the pharmacist will be able to:

- State the indication, mechanism of action, and adverse effects associated with dextromethorphan.
- Describe at least two potential reasons for the common misuse of dextromethorphan as it relates to its clinical effects.
- Name the four stages of associated with dextromethorphan toxicity and the corresponding anticipated symptoms.
- List management strategies that might be used in cases of acute dextromethorphan ingestion.

ACPE Activity Type: Knowledge-Based



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Over-the-counter (OTC) medications are often perceived by patients and health professionals as safer than prescription products. Reduced regulations and ease of access may drive some of these beliefs.¹ Unfortunately, these perceptions, as well as affordability, make some OTC products attractive substances of abuse. The antitussive dextromethorphan (DM) is an example of an OTC product that has of late become a common substance of abuse, particularly by adolescents.¹ Many abusers consider DM misuse more “socially acceptable” and safe compared with other commonly abused substances. Because of the OTC status of DM, pharmacists play critical roles as gatekeepers to drug access.

DM is a cough suppressant found in many combination cough and cold products that are also commonly coformulated with antihistamines and analgesics.^{1,2} DM was approved for clinical use by the Food and Drug Administration (FDA) in 1958.³ At

that time, the drug was available as a single-ingredient tablet under the brand name Romilar.³ Subsequently, Romilar was voluntarily removed from market as a result of concerns regarding drug diversion and abuse. Since that time, various manufacturers have introduced a range of DM products from syrups to gel tabs. Many of these varied dosage forms were developed with the intent of imparting unpleasant tastes that would discourage abuse.¹⁻³

Epidemiology

Since the introduction of DM in the 1950s, several cycles of abuse have been reported beginning with the withdrawal of Romilar. In 1986, the Swedish National Board of Health and Welfare moved DM into prescription status following reports of abuse-related deaths in two teenagers.⁴ More recently, the introduction of DM gel tabs in the 1990s resulted in a surge of reports of abuse and diversion.⁵ This surge was believed to be linked to the gel tab (e.g., DexAlone, Robitussin CoughGels) dosage forms, which provide a more concentrated and single-source supply of DM compared with existing and often coformulated liquid products.^{3,5,6} Shortly thereafter, FDA issued an opinion stating that the **scope and extent of DM abuse had not been fully elucidated and made no recommendations for altering the OTC status of the drug.**⁷ Between 2000 and 2003, the **American Association of Poison Control Centers Toxic Exposure Surveillance System data revealed an approximate 300% increase in the abuse of DM among adolescents 13 to 19 years of age.**⁸ In 2005, FDA responded to reports of five teenage DM-related deaths by issuing a warning letter outlining the potential deleterious effects of DM abuse.⁹

In 2005, results from the Partnership Attitude Tracking Study indicated that 45% of teens believed that abusing cough medicines was risky, up from 40% in 2004.¹⁰ Actual reported use of cough products for the purposes of “getting high” remained stable at 9% in 2004 and 10% in 2005. Responding to increasing trends toward DM abuse, an item related to the abuse of cough and cold medications was added to the University of Michigan Monitoring the Future survey in 2006.¹¹ At that time, the proportion of students reported having used these drugs during the previous year for the purposes of getting high were 4%, 5%, and 7% in grades 8, 10, and 12, respectively. These rates remained essentially the same in 2007, with the exception of use by 12th graders declining by 1% during the previous year.¹¹ Comparatively, marijuana use in 2007 fell by 1.4% (to 10.3%) in grade 8 and by 0.6% (to 24.6%) in grade 10 but increased by 0.2% (to 31.7%) among 12th graders.¹¹ **The Drug Abuse Warning Network report, which characterizes emergency department visits related to illicit drug use, reported that nonmedical use of DM accounted for 5,581 (44%) of the estimated 12,584 DM-related ED visits in 2004.** One-half of these nonmedical visits involved patients aged 12 to 20 years.¹² Ethanol was a coingestant in approximately 13% of these non-

At a Glance

Synopsis: Dextromethorphan (DM)—a relatively inexpensive and easily accessible over-the-counter (OTC) medication intended for use as an antitussant—has in recent years been increasingly used for illicit purposes, particularly by adolescents. Because DM is a common ingredient in many OTC cough and cold medications, many abusers consider DM misuse more “socially acceptable” and safe compared with other commonly abused substances. At clinical doses, the drug produces no euphoriant, analgesic, or dependence-producing effects. However, when ingested in large quantities, DM can produce respiratory depression, tachycardia, and hypertension, and other symptoms, and adverse effects may result from coingestion of combination drug components, including sympathomimetic amines (e.g., pseudoephedrine) and highly anticholinergic antihistamines (e.g., chlorpheniramine). Symptoms produced by most ingestions of DM are short lived and can be managed with observation and supportive measures.

Analysis: *Because most DM is accessed via OTC product purchase, pharmacists play an important role in controlling the availability of this potential substance of abuse. Although the drug is typically abused as a component of well-recognized cough and cold formulations, bulk-powder DM can be accessed from online companies or the drug can be synthesized as a free base. Given the abuse potential of DM, clinicians should be cognizant of patients purchasing the drug frequently or in large quantities. Policy makers are currently exploring methods for increasing awareness of DM misuse, controlling drug availability, and improving recognition of cases involving abuse.*



medical DM-related visits among patients aged 12 to 17 years and in 36% of such visits for those aged 18 to 20.¹²

A lesser-known use for DM is in the adjunctive management of pain, particularly in cases of cancer.^{13,14} In this realm, DM has been used in both acute and chronic pain treatment. Based on very limited research in this area, DM (30–90 mg) appears to be more efficacious when used to manage acute rather than chronic pain.^{13,14} Regardless of the type of pain involved, caution should be exercised in terms of abuse potential because this population will likely be receiving combination regimens involving both opioids and DM.

Availability

As previously stated, DM is available in various dosage forms. The availability of various product lines also differs from country to country. This review will focus on products available primarily in the United States. Although DM may be abused in a variety of dosage forms, the Coricidin product line appears especially favored by abusers,¹⁵ probably because these products contain a higher concentration of DM per unit dose. Abusers often refer to Coricidin abuse as “sheeting” because normal practice is to consume entire blister pack sheets of the drug to produce an effect.⁶ Several slang names for DM exist, including CCC, Triple C, DXM, Dex, Poor Man’s PCP, Skittles, and Robo. Many of these terms refer to DM-containing brand-name products.^{1,3,6,15}

DM also is available from various sources, including the Internet, in a pure bulk-powder form.¹⁴ DM in powder form is especially attractive to abusers because it enables them to avoid the unpleasant taste and potential adverse effects associated with combination drug products.^{3,6,16} The powder form also allows abusers to more readily consume DM in higher dosages. During the last session of Congress, a bill restricting the sale of bulk DM powder directly to consumers (Dextromethorphan Distribution Act of 2007) was introduced into the U.S. Senate.¹⁷

Some simple “recipes” for the free-base extraction of DM from OTC cough and cold products exist and are readily available via the Internet. One such process is known as the “Agent Lemon” technique.¹⁸ Because the free-base form of DM yielded by Agent Lemon and other techniques is often crystalline in nature, these products are sometimes referred to as “Crystal Dex.” The Agent Lemon technique involves a two-phase acid–base reaction. Typically, a DM-containing cough–cold product is mixed with ammonia to yield the precipitation of a lipophilic DM solvent. Lighter fluid is then added to the solvent to resolubilize the DM base in a lipid bilayer. The water portion of the mixture, which contains alcohol, coloring agents, and other hydrophilic components, is then discarded. Citric acid (usually in the form of lemon juice) is then added to the solvent layer to form the polar compound DM hydrochloride. Any remaining lipid base is then discarded. The remaining solution is known as Agent Lemon and can then be heated to form crystals or, in some instances, sugar is added to form a more palatable lemonade-like syrup.¹⁸

Pharmacology and pharmacodynamics

DM is a nonopioid synthetic analog of codeine that has long been recognized as an effective antitussant.^{3,6} The drug is the dextro-isomer of levorphanol and acts centrally within the medulla oblongata to raise the cough threshold.¹ Its specific actions are modulated by central sigma receptor binding.^{1,3,6} Unlike most opioids, the drug is devoid of activity at mu and delta receptors. When used as an antitussive, typical adult and pediatric doses (>12 years of age) of DM range from 60 to 120 mg/day in divided doses.¹⁹ In children older than 2 years, doses range from 2.5 to 10 mg administered up to four times daily. DM is currently not recommended for use in children younger than 2 years.²⁰ The drug is rapidly absorbed from the gastrointestinal tract with maximum serum concentrations occurring within 2.5 hours and a duration of action ranging from 3 to 6 hours.⁶ At clinical doses, the drug produces no euphoriant, analgesic, or dependence-producing effects.¹

Following absorption, DM undergoes first-pass metabolism before being excreted in the urine. The drug is metabolized by the cytochrome P450 (CYP) 2D6 system with a half-life of approximately 2 hours.²¹ The hepatic metabolism of DM may vary among individuals as a result of genetic polymorphisms that affect *O*-demethylation of the drug.^{21,22} The majority (85%) of individuals in the United States are rapid metabolizers with extensive CYP2D6 activity.^{21,22} **Impaired or slow metabolism of DM is believed to be an autosomal-recessive trait.**^{21,22} Interestingly, the drug is commonly used as a model in the study of polymorphisms involving a number of pharmacologic substrates.²³ **Dextrophan is the major active metabolite of DM and, like phencyclidine and ketamine, can noncompetitively antagonize the *N*-methyl-D-aspartate (NMDA) receptor.**³ **Antagonism of the NMDA receptor by dextrophan is believed to be the cause of the neurobehavioral effects commonly sought by DM abusers.**³ **Rapid metabolizers are prone to accumulating dextrophan quickly and may be more susceptible to the psychotropic effects of DM.**^{3,6,21,22} DM also appears to have some agonistic effects at serotonin receptors, which may also contribute to its abuse potential.²⁴

Clinical effects

Ingesting large doses of DM will result in several psychotropic effects, primarily as a result of accumulation of the active metabolite dextrophan.^{21,22} Symptoms have been described to occur in stages or steps (Table 1).³ **Initially, abusers report mild stimulant effects followed by hallucinations and delusions.**^{3,6} **Subsequently, abusers report development of feelings of dissociation often described as “out-of-body” experiences similar to those often associated with phencyclidine and ketamine.**³ **These effects are often accompanied by feelings of euphoria, ataxia, restlessness, and loss of concentration.**⁶ **Typically, these symptoms occur at DM doses greater than 2 mg/kg, with higher doses (>7 mg/kg) producing more dissociative effects.**²⁵



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Table 1. Stages of dextromethorphan toxicity^{1,3,6,21,22}**Stage 1 (1.5–2.5 mg/kg)**

- Increased alertness
- Restlessness
- Visual and auditory sensitization
- Generalized euphoria

Stage 2 (2.5–7.5 mg/kg)

- Exaggerated auditory and visual sensations followed by periods of deprivation
- Imbalance
- Hallucinations
- Increased energy and excitability

Stage 3 (7.5–15 mg/kg)

- Visual and auditory disturbances
- Periods of semiconsciousness
- Delayed reaction and response time
- Impaired cognitive ability
- Mania and/or panic
- Partial disassociation

Stage 4 (>15 mg/kg)

- Complete disassociation
- Hallucination/delusions
- Ataxia

In severe acute ingestions, various adverse effects have been reported, including nystagmus and mydriasis.^{1,3,6} Because DM is known to antagonize serotonin receptors, clinicians should be cognizant of the possibility for serotonin syndrome, which may be characterized by a variety of symptoms, including altered mental status, rigidity, hyperthermia, and seizures.^{1,24} In cases of massive DM ingestion, respiratory depression, tachycardia, and hypertension have been documented.¹ Liquid preparations of DM may possess a higher propensity to induce gastrointestinal symptoms as a result of ethanol-based diluents. Other symptoms and adverse effects may result from the unintentional coingestion of combination drug components, including sympathomimetic amines (e.g., pseudoephedrine) and highly anticholinergic antihistamines (e.g., chlorpheniramine).^{1,3,6,15} These symptoms can include tachycardia, hypertension, hyperthermia, mydriasis, and urinary retention.

When found in a cough and cold product, DM is usually formulated as “dextromethorphan hydrobromide.” Some clinicians have advised of the possibility of acute bromide toxicity in association with substantial DM ingestions.²⁶ Bromide toxicity is very rare and scantily described in the literature. Typically toxicity is evident at serum bromide levels greater than 50 to 100 mg/dL.²⁷ Acute toxicity may be associated with central nervous system depression, hypotension, and tachycardia. Chronic ingestion may result in a “bromism” syndrome, which is characterized by

behavioral changes, irritability, and lethargy. No specific antidote exists for bromide toxicity. Therapeutic measures usually include aggressive hydration with normal saline to promote urinary excretion and, in severe cases, hemodialysis.^{26,27}

Management

Given the profile of DM intoxication and its availability in coformulation with other products, recognizing ingestions may be difficult in the absence of a clear and targeted history. **Sources recommend emergency department referral in cases for DM ingestion at doses greater than 7.5 to 10 mg/kg.**²⁸ Rapid and definitive laboratory-based testing is not available in most hospital laboratories. Urine toxicology screens are particularly deficient in their ability to detect the presence of DM.⁶ Of note, massive ingestions of DM may cross-react and result in false-positive immunoassays for phencyclidine.^{29,30} In addition to a standard toxicology screen, basic laboratory assessment in cases of suspected DM ingestion should include serum electrolytes, hepatic transaminases, blood gases, and serum creatine phosphokinase.³ The bromide component of DM may result in falsely elevated levels of chloride because most autoanalyzers cannot differentiate between the two electrolytes.²⁶

Most symptoms resulting from ingestions involving DM are short lived and manageable with observation and supportive measures.^{1,3,6,28} This also includes the adverse effects associated with commonly coingested cough and cold products. Fatal outcomes following the ingestion of even massive amounts of DM alone are rare. Wolfe and Caravati²⁷ reported the case of a 23 year old man complaining of hallucinations following the ingestion of 2,160 mg (31 mg/kg) DM. The patient was administered activated charcoal, naloxone, and thiamine and subsequently discharged following an overnight admission for observation.

No specific antidote for DM intoxication exists. **Charcoal is known to adsorb opiates and would be expected to bind DM.**²⁸ Other standard decontamination procedures such as emesis and gastric lavage also would be expected to be effective means of reducing DM absorption from the gastrointestinal tract if performed in a timely fashion.²⁸ However, the risk of sedation and movement disorders associated with DM might preclude attempting these interventions because of the risk of aspiration.^{1,3,6} Also, given the effects of DM abuse, patients are unlikely to present for care before considerable concentrations of the drug have been absorbed from the gastrointestinal tract.

The use of naloxone in managing DM toxicity has been debated due to conflicting reports regarding its effectiveness.^{31–33} **Although no contraindications to the use of naloxone exist, its potential to reverse the symptoms of DM intoxication is questionable. When used, naloxone should be given at the standard doses recommended for managing opioid ingestions (e.g., 0.4–2 mg I.V. repeated every 2–3 minutes until response is achieved to a maximum dose of 10 mg).**^{27,28}

In managing DM ingestions, consideration also should be



Table 2. Dextromethorphan major drug–drug interactions^{1,34}

- Selective serotonin reuptake inhibitors
- Linezolid
- Monoamine oxidase inhibitors
- Sibutramine

given to the potential for adverse outcomes from drug–drug interactions (Table 2). Of particular risk is the combination of high doses of DM with other serotonergic drugs, including selective serotonin reuptake inhibitors, monoamine oxidase inhibitors), and certain antibiotics (e.g., linezolid).¹ These combinations may predispose patients to developing serotonin syndrome.³⁴ As previously mentioned, clinicians should also be cognizant of coformulated cough and cold products (e.g., antihistamines, sympathomimetics) and the adverse effects that these medications may cause when ingested in high concentrations. Acetaminophen is a particularly common agent found in DM coformulations and should be given particular attention because of the risk of hepatotoxicity and hepatic failure. Also, DM may be ingested in combination with other substances of abuse, including heroin, morphine, and other opiates. Ethanol-related intoxication also is possible, as many DM products use ethanol as a delivery vehicle. Although the total concentration of ethanol consumed may seem marginal, the potential for adverse effects, including the development of Wernicke–Korsakoff syndrome in thiamine-deficient patients, exists.^{3,28}

Although tachyphylaxis has been described among chronic users, drug dependence is rare.^{1,3,6,35,36} Animal and human studies have demonstrated little to no addiction potential.^{1,3,6} Chronic and/or excessive abusers may experience a psychological withdrawal syndrome, especially following abrupt discontinuation of the drug.^{35–37} Some patients with extensive abuse history, however, may require admission to detoxification programs.

Conclusion

OTC access, affordability, and perceptions of safety have potentially served as impetuses to the increased abuse of DM. The drug is typically abused as a component of well-recognized cough and cold formulations. However, bulk-powder DM can be accessed from online companies or the drug can be synthesized as a free base.^{16,18} DM's clinical effects vary according to genetic polymorphisms in metabolism and with increasing doses.^{21,22} Most abusers seek the dissociative effects of the drug, which are typically achieved with doses exceeding 2 mg/kg.²⁵ Managing acute intoxication is primarily supportive, with naloxone playing a potential role.^{27,28} Because most DM is accessed OTC, pharmacists serve a critical role in controlling the availability of this potential substance of abuse.⁶ According to anecdotal

reports, some pharmacies and health systems have placed DM behind the pharmacy counter, requiring a pharmacist to personally dispense the product and thus allowing for greater monitoring and control of drug availability. Clinicians should be aware of the abuse potential of DM and cognizant of patients purchasing the drug in large quantities or on a frequent basis. Additionally, implications may exist for policy in this area that might increase awareness of this drug misuse issue, control drug availability, and improve recognition of cases involving abuse.

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- Which of the following is not a potential contributor to the abuse of dextromethorphan (DM)?
 - Over-the-counter status
 - Low cost
 - Ease in access
 - Availability of drug-detection assays
- Among which of the following age groups is DM abuse considered the most common?
 - 9–12 years
 - 13–19 years
 - 20–30 years
 - 31–38 years
- The slang term *sheeting* refers to which of the following practices?
 - Layering DM syrup on sheets of wax paper for drying
 - Consuming entire sheets of DM-containing dosage forms available in blister packs
 - Diverting DM single-ingredient tablets from clandestine laboratories
 - Consuming DM in combination with other drugs that are expected to augment the clinical effects of the drug
- Which of the following best describes DM?
 - Opioid agonist of mu receptors
 - Nonopioid synthetic analog of codeine
 - Synthetic isomer of ketamine
 - Natural phencyclidine derivative
- Which of the following is true of rapid metabolizers of DM?
 - They comprise a majority of the U.S. population.
 - They are less prone to the psychotropic effects of DM.
 - Rapid metabolizers would be expected to produce less dextrophan compared with slow metabolizers.
 - All of the above alternatives are correct.
- A.A. is an 18-year-old white man known to be a DM abuser who presents with symptoms that include stupor and beliefs that he is having an out-of-body experience. With which of the following stages of DM toxicity are these complaints consistent?
 - Stage 1
 - Stage 2
 - Stage 3
 - Stage 4
- B.B. is a suspected DM abuser who presents to care with her parents, who request a serum drug screen. The screen is positive for DM, acetaminophen, phenylephrine, bromide, and diphenhydramine. What is the best explanation for these results?
 - B.B. is attempting suicide with acetaminophen ingestion.
 - B.B. is likely ingesting DM from coformulated products.
 - B.B. abuses a wide range of commonly misused drugs.
 - B.B. is attempting to mask her DM abuse with other agents.
- Parents notice that their son, C.C., a 16-year-old white adolescent, is ataxic and confused. His speech is slurred and confused, and his breathing is slightly labored. Two empty bottles of Robitussin DM are found by his bed. He was previously seen at dinner 3 hours earlier. He is transported to the emergency department. Which of the following is an appropriate intervention?
 - Gastric lavage
 - Administering activated charcoal
 - Administering a single dose of naloxone
 - Administering syrup of ipecac



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9. D.D. is a 19-year-old white man with a history of extensive drug abuse and severe depression. He is currently prescribed sertraline, hydroxyzine, and buspirone. Although D.D. is enrolled in a recovery program, he often abuses DM because he believes that it is “safer” than other drugs of abuse. Which of the following is a major risk in this patient?
- Serotonin syndrome
 - Rhabdomyolysis
 - QT interval prolongation
 - Status epilepticus
10. E.E. is a 25-year-old white man with a history of ethanol abuse who recently began abusing DM after having used the drug to treat a chronic cough. Previously, E.E. had no history of substance abuse other than ethanol. Which of the following might explain why this patient has begun abusing DM?
- DM is known to potentiate ethanol by inhibiting its metabolism.
 - DM is often coformulated with ethanol as a diluent.
 - Ethanol abuse is a known risk factor for DM misuse.
 - Ethanol is known to mask the ability for drug assays to detect DM.

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Selective serotonin reuptake inhibitor-induced akathisia

Lindsey P. Koliscak and Eugene H. Makela

Abstract

Objective: To review available information in the literature about akathisia (inner restlessness) caused by the selective serotonin reuptake inhibitors (SSRIs).

Data sources: Databases searched included Medline, PsychInfo, the International Pharmaceutical Abstracts, and Google Scholar. Search terms included *drug-induced akathisia, psychomotor agitation, drug-induced side effect, movement disorders, and extrapyramidal symptoms*. These search terms were cross-referenced with *selective serotonin reuptake inhibitors* and each of the currently marketed SSRIs: *fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, and escitalopram*.

Study selection: Relevant articles were chosen if they specifically mentioned the word akathisia. Case reports were chosen based on a clear view that an SSRI was a contributing or causative agent of akathisia.

Data synthesis: Recognizing akathisia is important because it can be very bothersome and may cause suicidal ideations. Akathisia can be recognized by examining symptoms, looking at predisposing factors, and using the Barnes Akathisia Rating Scale (BARS). Predisposing factors include use of multiple akathisia-inducing drugs, recent increases in SSRI dose, previous development of akathisia, baseline psychiatric disorders, and brain trauma. Treatment options include the addition of a centrally acting beta-blocker, a benzodiazepine, or an anticholinergic agent.

Conclusion: Pharmacists can play an active role in recognizing akathisia by being aware of its characteristics, conducting a thorough medication history to identify causative agents, and using BARS to evaluate patients. These efforts may preclude unnecessary discomfort for the patient and reduce the potential for nonadherence induced by akathisia.

Keywords: Akathisia, adverse drug effects, serotonin receptor modulators, pharmacotherapy.

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Learning objectives

At the conclusion of this program, the pharmacist will be able to:

- State subjective and objective characteristics of akathisia.
- List four to six factors that may predispose patients to developing akathisia while taking a selective serotonin reuptake inhibitor (SSRI).
- Describe three classes of drugs that can be used to treat akathisia associated with SSRIs.
- Name a rating scale that can be used to identify presence and measure severity of akathisia in the pharmacy setting.

ACPE Activity Type: Knowledge-Based



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Common adverse effects, including sexual dysfunction, nausea, insomnia, or headache, have a well-established association with selective serotonin reuptake inhibitors (SSRIs). A less acknowledged adverse effect is akathisia, which is derived from a Greek term meaning “not to sit.”¹ It can be extremely discomforting to the patient and warrants attention.

Akathisia induced by SSRIs is classified by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (text revision), as “Medication-Induced Movement Disorder Not Otherwise Specified.” It demonstrates no variation in presentation to the more commonly identified “Neuroleptic-Induced Acute Akathisia.”²⁻⁴

Databases searched included Medline, PsychInfo, the International Pharmaceutical Abstracts, and Google Scholar. Search terms included *drug-induced akathisia*, *psychomotor agitation*, *drug-induced side effect*, *movement disorders*, and *extrapyramidal symptoms*. These search terms were cross-referenced with *selective serotonin reuptake inhibitors* and each of the currently marketed SSRIs: *fluoxetine*, *fluvoxamine*, *sertraline*, *paroxetine*, *citalopram*, and *escitalopram*. Relevant articles were chosen if they specifically mentioned the word akathisia. Case reports were

chosen based on a clear view that an SSRI was a causative or contributing agent.

Presentation

Akathisia is most often referred to as a feeling of inner restlessness, but many patients may be unable to describe this feeling unless asked directly.⁵ Instead, patients sometimes confuse it with feelings of anxiety or agitation. An author of the current report (Dr. Makela) had a patient describe this feeling as “an itch inside that I can’t scratch.” In a case presented by Walker,⁶ the patient described feelings of “wanting to jump out of my skin.” Altshuler et al.⁷ described a patient who referred to akathisia as a “crawling skin sensation.” Objectively, patients will often be unable to sit still and may be observed persistently swinging their feet or crossing and uncrossing their legs while seated.⁸ Both subjective and objective criteria as described above are essential in the diagnosis of akathisia.⁹

SSRI-induced akathisia most often develops within several days to weeks upon administration or dosage increase (Table 1). Olivera¹⁰ described a patient whose akathisia occurred within a mere 2 hours of taking a dose of sertraline. In contrast, Akagi and Kumar¹ presented a patient who developed akathisia 4 weeks after a dosage increase of fluoxetine. These findings suggest interpatient variability regarding the development of akathisia in response to exposure time.

Importance of recognition

Akathisia is not always easy to recognize. Many patients taking SSRIs have preexisting psychiatric disorders, and misinterpreting akathisia symptoms can occur easily. These symptoms may be mistaken for agitated depression, anxiety, withdrawal, bipolar disorder, worry, or even restless leg syndrome.^{1,3,8,11-13} Misdiagnosing akathisia as an underlying psychiatric disorder could lead to an increase in dosage of the offending agent or the addition of a new, unnecessary medication such as an antipsychotic. Consequently, an exacerbation of akathisia symptoms would likely be observed. For example, Walker⁶ reported a case of a 21-year-old man initiated on sertraline for depression. He developed akathisia, which was misdiagnosed as an anxiety disorder. The patient’s sertraline dose was doubled in response, and his symptoms got worse. The patient was then changed to paroxetine, which also failed to improve his symptoms. After proper diagnosis of akathisia by a psychiatrist, he discontinued paroxetine, and his symptoms resolved. Early recognition of akathisia is imperative for preventing unnecessary distress in patients taking SSRIs.

Rates of akathisia relating to fluoxetine have been projected to range between 9.8% and 25%.³ In a prospective experimental study performed by Kurzthaler et al.,¹⁴ 40 elderly patients with depression but without comorbid psychiatric conditions were given an SSRI to assess adverse effects and efficacy in this population. These SSRIs included sertraline, paroxetine, citalopram, and fluoxetine. Five of these patients (12.5%) developed akathisia

At a Glance

Synopsis: Pharmacists can play a pivotal role in identifying akathisia—an inner restlessness that can be caused by the selective serotonin reuptake inhibitors (SSRIs)—by examining symptoms and predisposing factors and using the Barnes Akathisia Rating Scale. Symptoms of akathisia may be mistaken for agitated depression, anxiety, withdrawal, bipolar disorder, worry, or even restless leg syndrome. Recognizing akathisia is critical because it can be very distressful to patients and may cause suicidal ideations. Use of multiple akathisia-inducing drugs, recent increases in SSRI dose, previous development of akathisia, baseline psychiatric disorders, and brain trauma are among predisposing factors for akathisia. Beta-blockers and benzodiazepines are well-established treatment options for the condition.

Analysis: Although akathisia is often characterized as an extrapyramidal symptom (EPS), reports in the literature suggest varying underlying pathways. EPSs are suggested to result from a dopamine deficiency in the nigrostriatal, as opposed to mesocorticolimbic, pathway. Propranolol has been shown to be efficacious in treating akathisia but not EPSs, providing further evidence that different mechanisms are involved in akathisia etiology. However, without further support for these mechanisms, akathisia will likely remain classified as an EPS. Pharmacists can play a key role in recognizing treatment-emergent akathisia and take actions on behalf of patients experiencing its debilitating symptoms.



Table 1. A review of case reports of SSRI-induced akathisia

SSRI	Total daily dose	Age (years)	Gender	Exposure time before onset	Treatment	Other risk factors	Study
Fluoxetine	20 mg	40	Female	"Few days"	Discontinuation and change to nefazodone		C. helben ⁴¹
Fluoxetine	20 mg	63	Female	3 days	Discontinuation and change to nortriptyline	Cerebral atrophy and multiple brain infarcts, medical history of bipolar disorder	Arya ³⁷
Fluoxetine	20 mg	35	Female	12 hours	Addition of propranolol 60 mg		Lipinski ³
Fluoxetine	20 mg	—	Female	3 weeks	Discontinuation and change to nortriptyline	Previous exposure to desipramine, history of panic attacks	Hamilton ¹⁸
Fluoxetine	20 mg	15	Male	3 weeks	Change to escitalopram 5 mg		Schaller ⁴⁰
Fluoxetine	20 mg	47	Female	14 days	Discontinuation and change to paroxetine 80 mg (tapered increase)		Bauer ⁴
Fluoxetine	40 mg	30	Female	2 days	Addition of propranolol 90 mg	Previous symptoms of akathisia with use of haloperidol and perphenazine	Lipinski ³
Fluoxetine	40 mg	22	Female	3 weeks at increased dose	Discontinuation plus propranolol 20 mg three times a day	Recent increased dose	Hansen ²⁰
Fluoxetine	40 mg	62	Male	4 weeks at increased dose	Discontinuation plus diazepam 2 mg twice a day for 1 week	Previous symptoms of akathisia with use of metoclopramide and recent increased dose of fluoxetine	Akagi ¹
Fluoxetine	60 mg	22	Male	5 days	Single dose of propranolol 40 mg	High dose of fluoxetine	Lipinski ³
Fluoxetine	60 mg	18	Female	5 days	Addition of propranolol 60 mg	High dose of fluoxetine	Lipinski ³
Fluoxetine	80 mg	26	Female	7 days	Addition of propranolol 60 mg	Previous symptoms of akathisia with use of neuroleptics, high dose of fluoxetine	Lipinski ³
Fluoxetine	80 mg	54	Female	4 days	Discontinuation and change to paroxetine 40 mg	Concurrent use of nortriptyline, high dose of fluoxetine	Bauer ⁴
Paroxetine	20 mg	40	Female	14 days	Discontinuation and change to nefazodone		Chelben ⁴¹
Paroxetine	20 mg	18	Female	6 days	Addition of propranolol 20 mg twice a day		Baldassano ¹²



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Paroxetine	20 mg	63	Male	7 days	Addition of propranolol 80 mg (titrated) and clonazepam 1.5 mg (titrated)	History of panic disorder, increase in dose from 10 to 20 mg on day 4	Adler ³⁶
Paroxetine	20 mg	83	Male	10 days after addition of risperidone	Discontinuation of paroxetine (taper), electroconvulsive therapy, and change to nefazodone	Recent addition of risperidone	Hansen ¹⁹
Sertraline	25 mg	18	Female	3 days	Addition of propranolol 10 mg twice a day		Klee ⁴⁶
Sertraline	50 mg	54	Female	3 days	Discontinuation of sertraline		Olivera ¹⁰
Sertraline	50 mg	21	Male	14 days	Discontinuation of sertraline	No	Walker ⁶
Sertraline	50 mg	34	Female	"Few days"	Discontinuation plus addition of lorazepam 0.5 mg three times a day as needed	Previous symptoms of akathisia with use of haloperidol, history of bipolar disorder with psychotic features	Opler ³²
Sertraline	50 mg	22	Female	2 days	Discontinuation and change to tricyclic agent	Brain trauma, previous haloperidol use, anxiety	Hensley ¹¹
Sertraline	50 mg	35	Female	7 days	Discontinuation and addition of alprazolam	History of panic attacks, depression, and previous suicide attempt	Settle ²¹
Sertraline	50 mg	48	Female	3.5 weeks	Discontinuation, four day course of clonazepam 0.5 mg twice a day, and change to phenelzine sulfate 60 mg	Previous use of clomipramine and concomitant use of trazodone	Altshuler ⁷
Sertraline	100 mg	28	Female	2 hours after taking increased dose	Decreased dose to 50 mg	Recent increase in dosage from 50 to 100 mg	Olivera ¹⁰
Sertraline	150 mg	78	Female	"Few days"	Discontinuation and change to clomipramine	Previous use of clomipramine, high dose of sertraline	Hoaken ⁴⁵
Sertraline	200 mg	35	Male	3 days after taking increased dose	Discontinuation and change to nortriptyline	Previous subarachnoid hemorrhage due to arteriovenous malformation in corpus callosum, high dose of sertraline	Shihabuddin ³⁰
Fluvoxamine	300 mg	38	Male	7 days after taking increased dose	Addition of trihexyphenidyl 2 mg and propranolol 60 mg	Obsessive compulsive disorder and kleptomania, recent increase in dosage from 200 mg, high dose of fluvoxamine	Chong ²³
Citalopram	20 mg	Adolescent	NA	NA	Akathisia resolved without intervention after 3 weeks on citalopram		Seedat ³⁵

Abbreviations used: NA, not available; SSRI, selective serotonin reuptake inhibitor.



and were withdrawn from the study by day 14. Leo¹⁵ performed a Medline review of movement disorders associated with SSRI use and found that 32 of 71 reported movement disorders were akathisia. However, other sources have reported much lower rates of SSRI-induced akathisia. Spigset¹⁶ reported only seven cases of akathisia in 1,202 reports of adverse events to SSRIs. Schillevoort et al.¹⁷ reviewed adverse drug reactions of SSRIs to find out if there was an association between this drug class and extrapyramidal symptoms (EPSs). He found 61 cases of EPSs with SSRI use, and only one of these cases reported akathisia.

Suicide attempts may be prompted in patients taking SSRIs as a means to end the restlessness that akathisia provokes. Hamilton and Opler¹⁸ presented a case of a woman, stating, "Although her mood was good, she was afraid that she would kill herself because of these restless and out-of-control feelings." In another case, an 83-year-old man experiencing akathisia described it as "a restless nightmare," and if it didn't stop, he'd "rather be dead."¹⁹ Hansen²⁰ described a case of a 22-year-old woman who developed akathisia and "elaborate suicidal ideation revolving around her own violent death" after taking an increased dose of fluoxetine. In another case, after 3 weeks of sertraline therapy, a patient with akathisia attempted suicide to "escape from the profound discomfort and restlessness."²¹ These cases suggest that akathisia-induced suicidal thoughts may present as a way to end the restlessness and that patients do not have a true desire to die. Hamilton and Opler¹⁸ have proposed that health professionals should refer to suicidal thoughts induced by akathisia as an "extrapyramidal-induced dysphoric reaction," as opposed to "suicidal ideation" in an effort to stress the difference.

Etiology

Although speculation exists, akathisia may result from a deficiency of dopamine in the brain. Reports in the literature suggest that this deficiency is caused by serotonergic-induced inhibition of dopamine in the mesocorticolimbic pathway projecting from the ventral tegmental area (VTA) of the brain to the prefrontal cortex.^{3,5} Like serotonin, noradrenalin acts similarly to inhibit dopamine in the VTA.³ Therefore, drugs increasing the stimulation of serotonergic or noradrenergic receptors in this pathway could theoretically induce akathisia, as proposed by Lipinski et al.³ Lane suggested that this mechanism is supported by the fact that medications used to treat akathisia (e.g., propranolol) have been found to increase dopamine in the mesocorticolimbic pathway.⁵

Although akathisia is often characterized as an EPS, reports in the literature suggest varying underlying pathways. EPSs are thought to arise from a dopamine deficiency in the nigrostriatal pathway, as opposed to the mesocorticolimbic pathway.^{5,18} Further evidence that different mechanisms are involved, as proposed by Hamilton and Opler,¹⁸ is suggested by propranolol being proven efficacious in treating akathisia but not in treating EPSs. Without further support for these mechanisms, akathisia will

likely remain classified as an EPS.

Diagnosis

The Barnes Akathisia Rating Scale (BARS)²² can be used to assess a patient with suspected akathisia. This scale, developed in 1989 by Thomas Barnes, measures the subjective and objective aspects of akathisia. For the objective portion, the evaluator rates the amount of movement the patient displays on a scale from 0 (normal) to 3 (inability to remain still). The subjective portion is divided into two parts, awareness of restlessness and distress related to restlessness, both of which are measured on a scale from 0 (absence of restlessness/no distress) to 3 (awareness with extreme compulsion to move/severe distress). A rating of 0 on either of the subjective sections does not represent akathisia and may be described as "pseudoakathisia." The objective and subjective portions are summed to yield a value of 0 to 9; a higher score represents more severe akathisia. The administrator may also assign a global assessment rating, ranging from 0 (absent akathisia) to 5 (severe akathisia).^{9,22}

Predisposing factors

Reports from the literature have suggested several risk factors for developing akathisia (Table 2). The use of multiple akathisia-inducing drugs, a sudden increase in SSRI dose, and a previous history of akathisia may predispose patients to developing akathisia with SSRIs. The half-life and anticholinergic properties of individual SSRIs also may affect the risk of developing akathisia. Patients with baseline anxiety or panic conditions or patients with previous brain trauma appear to have increased reports of akathisia induced by SSRIs. Female sex also may be a predisposing factor for developing akathisia.

Antidopaminergic, serotonergic, or noradrenergic drugs are most commonly associated with akathisia (Table 3). Examples include antipsychotics (e.g., haloperidol),³ antiemetics (e.g., metoclopramide, prochlorperazine),¹ and antidepressants (e.g., tricyclic agents,⁷ SSRIs,²⁰ venlafaxine²³). Patients taking any of the above agents concurrently with SSRIs are at an increased risk for developing akathisia. Possible cytochrome P450 (CYP) system enzyme inhibition may play a role when SSRIs are taken with other agents because many SSRIs are strong inhibitors.⁵ For example, fluoxetine and paroxetine are strong inhibitors of CYP2D6, and substrates of CYP2D6 include risperidone and haloperidol.²⁴⁻²⁷ Inhibition of CYP2D6 by fluoxetine or paroxetine would elevate levels of these two antipsychotics, leading to an increased risk of adverse effects like akathisia. For example, Hansen and Wilkinson¹⁹ reported a case of an elderly man taking paroxetine. When risperidone was added to his regimen, he developed akathisia approximately 10 days later.

Markkula et al.²⁸ compared patients taking antipsychotics with or without concomitant use of an SSRI. He began with three groups of patients taking antipsychotics. The three groups included patients using second-generation (atypical) antipsychot-



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ics (e.g., clozapine), oral first-generation (typical or conventional) antipsychotics (e.g., haloperidol), or first-generation antipsychotics (e.g., haloperidol) by depot injection. Each group was subdivided based on concomitant use of an SSRI, resulting in six groups total. Patients taking the atypical antipsychotic without an SSRI were considered the control group and were compared with the other five groups to assess significant differences. Regardless of SSRI use, both atypical groups showed no development of akathisia. In the groups taking the conventional orally administered antipsychotic, akathisia developed in 4.8% of patients who were not on an SSRI ($P = 0.55$) and in 21.4% of patients who were on an SSRI ($P = 0.081$). In the group taking the conventional antipsychotic administered by depot injection, akathisia developed in 33.3% of patients who were not on an SSRI ($P = 0.008$) and in 44.4% of patients concomitantly on an SSRI ($P = 0.008$).²⁸ Thus, simultaneous use of an SSRI increased the number of cases of akathisia for those on conventional antipsychotic therapy.

Sudden increases in dosage of SSRIs may potentiate the onset of akathisia. In fact, high doses of SSRIs in general are more likely to cause akathisia than low doses. In a case presented by Chong and Tan,²⁹ a patient's dose of fluvoxamine was increased from 200 to 300 mg/day and the patient developed akathisia within a week. Similarly, Shihabuddin and Rapport³⁰ reported a case of a patient who developed akathisia after the dose of sertraline was titrated over 2 weeks from 50 to 200 mg/day. Akathisia began after 3 days on the 200-mg dose.

Patients who have previously experienced akathisia induced by a non-SSRI drug may be more likely to reexperience it with an SSRI. Poyurovsky et al.³¹ presented a case of a patient with a history of akathisia induced by haloperidol. The patient developed the same symptoms of akathisia when he began fluvoxamine. Other cases in the literature refer to patients recognizing SSRI-induced

akathisia as comparable with previous incidents of akathisia induced by other causative agents.^{1,3,32}

Previous exposure to a medication that can cause akathisia may increase the risk of developing the condition upon introduction of a new SSRI, regardless of whether the patient actually developed akathisia while on the previous medication. Gerber and Lynd³³ examined 30 reported cases of SSRI-induced akathisia. Of these patients, 24 were either taking or had previously taken a neuroleptic.

Certain SSRIs may be more likely to cause akathisia than others. Each drug's affinity to the receptors involved in akathisia may vary.⁵ Bauer et al.⁴ presented two patients who developed akathisia while taking fluoxetine. After switching to paroxetine, the patients' akathisia resolved. The authors hypothesized that this difference may be caused by paroxetine's increased binding to cholinergic receptors. In their experience, Bauer et al. reported observing more anticholinergic adverse effects from paroxetine than from fluoxetine. They suggested that greater anticholinergic properties may reduce the risk for developing akathisia. They further supported this idea because anticholinergics have been effective in treating akathisia.^{4,29}

Some reports in the literature have suggested that SSRIs with a long half-life may also put patients at an increased risk for akathisia.^{5,15} In a review of the literature, Lane⁵ proposed that because of the long half-life of fluoxetine, "The use of higher-than-necessary dosages may be almost inevitable. It takes 6-8 weeks for fluoxetine and norfluoxetine to approach steady-state plasma levels." He went on to explain, "20 mg/day of fluoxetine as a starting dose may result in a relatively higher proportion of patients (eventually) receiving higher-than-necessary plasma levels to achieve or maintain antidepressant response compared

Table 2. Risk factors associated with SSRI-induced akathisia

- Use of multiple drugs that can cause akathisia (neuroleptics, SSRIs, antiemetics)^{4,19}
- Increase in SSRI dose/high dose^{1,3}
- Previous development of akathisia^{1,3,32}
- Previous exposure to potential akathisia-inducing drugs^{11,18}
- SSRIs with less anticholinergic activity⁵
- SSRIs with longer half-life⁵
- Baseline anxiety, agitation, panic disorders^{18,36}
- Brain trauma^{30,37}
- Female sex^{15,33}

Abbreviation used: SSRI, selective serotonin reuptake inhibitor.

Table 3. Medications associated with akathisia

Drug class	Examples
Selective serotonin reuptake inhibitors	Fluoxetine, ²¹ paroxetine, ⁴¹ sertraline ¹⁰
First-generation (typical) antipsychotics	Haloperidol, ³ perphenazine ²⁸
Antiemetics	Metoclopramide, ¹ prochlorperazine ¹
Second-generation (atypical) antipsychotics	Risperidone ¹⁹
Tricyclic antidepressants	Clomipramine ⁷
Selective norepinephrine reuptake inhibitors	Venlafaxine ²³



to other SSRIs.” Lane suggested that these higher plasma levels could result in late development of adverse effects and toxicity. Fluoxetine has an elimination half-life of 4 to 6 days, while its active metabolite norfluoxetine has an elimination half-life of 16 days.²⁴ Comparatively, the elimination half-life of escitalopram is 27 to 32 hours, while its primary metabolite desmethylcitalopram has an elimination half-life of 59 hours.³⁴ This may explain why far more cases of akathisia have been reported with fluoxetine than with escitalopram.

Gerber and Lynd³³ found that of 30 reported cases of akathisia induced by SSRIs, 60% of patients were taking fluoxetine. The remaining 40% of cases were split equally among those taking fluvoxamine, sertraline, and paroxetine. Leo¹⁵ found that 20 of 32 cases of SSRI-induced akathisia resulted from fluoxetine treatment, while the others were split among sertraline, fluvoxamine, and paroxetine. In the above-cited reviews, many patients were receiving other medications that could have contributed to the development of akathisia. The increased reports of akathisia induced by fluoxetine may be attributed to the fact that it is an older, more commonly used SSRI compared with its counterparts.²⁰ We found one case (Seedat et al.³⁵) that linked citalopram to akathisia and no cases associating escitalopram with akathisia. This may be because these drugs are newer to the market and cases have not been reported as frequently, or it could be due to the pharmacodynamic and pharmacokinetic properties as discussed above.

Patients who have anxiety, agitation, restlessness, or panic disorders before initiating SSRI therapy may be at an increased risk for akathisia.⁵ Olivera¹⁰ described three patients; two had baseline anxiety, and the other had baseline obsessive-compulsive disorder and panic attacks. All three patients developed akathisia with initiation of sertraline. Settle²¹ described a patient who experienced panic attacks throughout her life and developed akathisia upon sertraline administration. This predisposition has been exemplified in other cases throughout the literature.^{11,18,32,36}

Brain trauma may be another predisposing factor to SSRI-induced akathisia. Hensley and Reeve¹¹ presented the case of a 22-year-old woman who developed akathisia from trials of both sertraline and paroxetine. She was being treated for depression, anxiety, and pain resulting from a motor vehicle accident. This patient had sustained trauma to the head in the accident, and the authors of her case believed this may have predisposed her to developing akathisia. In a case presented by Arya,³⁷ a computerized scan of the brain of a 63-year-old woman revealed “multiple infarcts and generalized cerebral atrophy.” She developed akathisia within 3 days of fluoxetine initiation, leading to the conclusion that a “pre-existing compromised brain function” may be a risk factor for akathisia.

Whether sex plays a role in the development of akathisia remains unknown. In one review, 27 of 30 cases of SSRI-induced akathisia involved female patients.¹⁵ Gerber and Lynd’s³³ review

of movement disorders found similar results; 23 of the 30 cases of SSRI-induced akathisia involved female patients. Based on these cases, it appears that women may be more likely to develop akathisia. However, male patients reported akathisia in four of seven cases in Spigset’s¹⁶ review of akathisia caused by SSRIs, but this difference is likely insignificant because of the small number of cases. In a review of extrapyramidal reactions associated with SSRIs, Caley³⁸ noted that women experience the illnesses that SSRIs are used to treat more frequently than men; therefore, women would be more likely to experience the adverse effects.

Age does not appear to be a factor for developing akathisia. We found no trends in age for the cases found in the literature. Similarly, in a review of SSRIs and EPSs, including akathisia, no association with age was found.³⁸

Management

Several treatment options for akathisia exist (Table 4). As discussed below, adding a centrally acting beta-blocker such as propranolol appears to be the most frequently used therapy. Benzodiazepines and anticholinergic drugs serve as other treatment options. Another choice for treatment is to switch to an alternative antidepressant or to change to another SSRI. In some cases, akathisia may subside over time without treatment.

The addition of a beta-blocker to a patient’s regimen is an excellent treatment option to control akathisia. Propranolol is the centrally acting beta-blocker of choice and is most commonly administered at a dose of 40 to 60 mg/day (Table 1). Baldassano et al.¹² described a case of an 18-year-old woman who took paroxetine 20 mg/day for depression and developed akathisia in less than 1 week. Propranolol 20 mg was administered twice a day, and her akathisia improved within 4 days. When propranolol was discontinued 4 months later, the patient’s akathisia returned. Lipinski et al.³ described successful use of propranolol, ranging from 40 to 90 mg/day, in treating five patients with SSRI-induced akathisia. Propranolol can be added to control symptoms even if a patient discontinues the offending SSRI. Hansen²⁰ described a 23-year-old woman who developed akathisia after 3 weeks of taking a recently increased dose of fluoxetine. Her fluoxetine was stopped, and propranolol 20 mg three times a day was added, which solved the problem.

The addition of a benzodiazepine is another option for treating akathisia. In a fluoxetine-induced case of akathisia, the patient was treated successfully by taking diazepam 2 mg two times a day for 7 days and discontinuing fluoxetine.¹ Clonazepam, alprazolam, and lorazepam also have been reported to treat akathisia.^{7,21,32,36}

Anticholinergics also have been used to control akathisia, but less supporting evidence exists in the literature. Trihexyphenidyl 2 mg/day has been reported to successfully treat fluvoxamine-induced akathisia with simultaneous use of propranolol.²⁹ Anticholinergics would not be the best choice as first-line therapy.

Scant evidence suggests the efficacy of antiserotonergic agents in treating akathisia. Muly et al.³⁹ described a case of a



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Table 4. Treatment options for SSRI-induced akathisia

Suggestion	Recommendation
Addition of another medication	Centrally acting beta-blocker: propranolol 40–60 mg/day ^{3,20,29,36} Benzodiazepine: diazepam 2 mg/day, ¹ clonazepam 1.0–1.5 mg/day ^{7,36} Anticholinergic (less evidence supporting use): trihexyphenidyl 2 mg/day ²⁹
Discontinue offending SSRI and change to another drug class	Nefazodone (doses vary), ^{19,41} nortriptyline (doses vary) ^{18,37}
Try an alternative SSRI	Paroxetine, ⁴ citalopram, ³⁵ escitalopram ⁴⁰
Lower the dose of the offending SSRI	Titrate dose downward until results are seen ¹⁰

Abbreviation used: SSRI, selective serotonin reuptake inhibitor.

patient with akathisia who was being treated with multiple drugs including fluoxetine. The patient was administered cyproheptadine 12 mg, and his akathisia resolved. Poyurovsky et al.³¹ suggested mianserin 15 mg/day to alleviate akathisia. He found it to be successful in treating a patient with fluoxetine-induced akathisia unresolved with the use of biperiden. Although mianserin is not currently available in the United States, it is interesting to mention because of the pharmacologic mechanism. This drug class would not be recommended as first-line therapy for treating akathisia.

Substitution of the offending SSRI with a different SSRI may prove beneficial for some patients because of varying anticholinergic and/or pharmacokinetic properties, as previously discussed. Bauer et al.⁴ reported two cases of fluoxetine-induced akathisia in which substitution with paroxetine fixed the problem. Another case reported cessation of akathisia after a switch from fluoxetine to escitalopram.⁴⁰

Switching to another class of antidepressants is another treatment option. In two patient cases presented by Chelben et al.,⁴¹ the patients developed akathisia with paroxetine and fluoxetine use and nefazodone was substituted successfully. As suggested by Chelben et al.,⁴¹ this substitution is a good alternative because it eliminates the need for an additional medication. Hansen and Wilkinson¹⁹ described a case of an 83-year-old man who developed akathisia on paroxetine 20 mg daily. He was concurrently taking a low-dose risperidone. Paroxetine was changed to nefazodone, and his akathisia went away. Tricyclic antidepressants (e.g., nortriptyline) may be another alternative to an SSRI. Hamilton and Opler¹⁸ described one patient who developed akathisia after taking fluoxetine 20 mg for 3 weeks. She was changed to nortriptyline, and her akathisia disappeared.

Discontinuing the offending SSRI usually results in symp-

tom resolution when other options fail. Arya³⁷ described a case of fluoxetine-induced akathisia resistant to anticholinergic and benzodiazepine therapy. It was eventually eliminated upon discontinuation of fluoxetine.

Some cases suggest that akathisia may subside with time. Seedat et al.³⁵ reported a case of an adolescent who developed akathisia while taking citalopram 20 mg/day, and his akathisia subsided without intervention after 3 weeks. Olivera¹⁰ described three cases of sertraline-induced akathisia. In the first case, a 61-year-old woman was taking sertraline 50 mg/day. She developed restlessness, and her sertraline dose was increased to 100 mg/day. Her akathisia got worse, so her dose of sertraline was dropped back to the original 50 mg/day. Her symptoms improved, and she was akathisia free after 12 weeks. Olivera described two other cases involving similar events. He suggested that adverse reactions caused by sertraline may be “dose- and time-related.” Additionally, time-related decreases in adverse effect burden of sertraline were observed by Reimherr et al.,⁴² who performed a study observing the adverse effect profile of this drug. Akathisia has been proposed to be a component of the “jitteriness syndrome” often arising from the use of other antidepressants³; this syndrome has been found to diminish with time.⁴³ Of important note, although “spontaneous resolution”¹⁰ has been observed in certain instances, the potential consequences of akathisia may not remit over time in most cases.

Exercise may be beneficial as a nonpharmacologic therapy in alleviating akathisia. In one case, a set of exercise pedals was given to a patient, which helped relieve her “distressing urge to move” and allowed her to carry on with some normal functions as she pedaled.⁴⁴ Based on this case, initiating a “repetitive exercise” may make the symptoms of akathisia more tolerable.⁴⁴



Conclusion

Akathisia is not a benign adverse effect. The effect can be extremely egregious, and some reports have linked akathisia with suicidality. With the increasing use of medications from this drug class for a variety of indications, identification of predisposing factors, early recognition of akathisia, and proper management are imperative. Beta-blockers and benzodiazepines are well-established treatment options for akathisia.

Pharmacists can play an active role in recognizing akathisia by being aware of its characteristics and by conducting a thorough medication history to identify causative agents. Pharmacists in the community and hospital settings can use BARS to evaluate and identify suspected akathisia patients. If needed, recommendations to manage the condition can be provided to the patient's physician. These efforts may preclude unnecessary discomfort for the patient and reduce the potential for nonadherence induced by akathisia.

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Assessment Questions

Instructions: The assessment test for this activity must be taken online; please see “CPE Processing” below for further instructions. There is only one correct answer to each question. This CPE will be available online at www.pharmacist.com no later than March 31, 2009.

- A.B. is a 54-year-old woman who comes to your pharmacy regularly. You sit down to talk with her and observe her crossing and uncrossing her legs excessively. It appears that she can't sit still. She claims that she doesn't feel like herself lately and that she feels very anxious. She is currently taking simvastatin 20 mg daily and a multivitamin, and she recently had a dosage increase of fluoxetine to 40 mg daily. You suspect she has akathisia caused by her fluoxetine. Which of the following is most appropriate course of action?**

 - Contact her physician and tell him to discontinue her fluoxetine.
 - Use the Barnes Akathisia Rating Scale (BARS) to assess her symptoms.
 - Wait to see if she feels the same when she returns to get her prescriptions next month.
 - Tell her to call her doctor and make an appointment immediately because she has akathisia.
- E.F. is a 24-year-old man who recently started taking paroxetine 20 mg/day for depression. He also takes risperidone 2 mg daily, loratadine 10 mg daily, a multivitamin supplement, and a calcium supplement. What is one of E.F.'s risk factors for developing akathisia?**

 - Age
 - Sex
 - Concurrent use of risperidone
 - His dose of paroxetine
- R.S. is a 45-year-old man who recently began taking paroxetine 50 mg for depression. At the pharmacy today, he tells you that his paroxetine makes him feel “weird.” He describes feeling like “he just has to move around.” He tells you he's experienced this feeling before when he used to take haloperidol. He says that he was given a medication that proved helpful. You check his medication history and see that propranolol 20 mg twice a daily had been prescribed with his haloperidol. You evaluate him using BARS, and he scores a 6. What should you do next?**

 - Tell him to stop taking his paroxetine immediately.
 - Contact his doctor and tell him to increase his dose of paroxetine.
 - Tell him his symptoms will go away in a few days.
 - Contact his doctor and be prepared to recommend adding propranolol 40 mg daily to R.S.'s regimen.
- G.H. is a 55-year-old woman who comes to your pharmacy to fill a new prescription for propranolol 40 mg twice a day to treat her akathisia, which her doctor attributes to her fluoxetine. She tells you that she has been feeling very restless and jittery and that she just can't sit still. Which of G.H.'s symptoms are necessary for the diagnosis of akathisia?**

 - Her subjective symptom (inner restlessness)
 - Her objective symptom (inability to sit still)
 - Both her subjective and objective symptoms
 - None of these symptoms describe akathisia

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5. C.D. is an 80-year-old woman who gets all of her prescriptions at your pharmacy. Her caregiver drops off a new prescription for fluoxetine 20 mg daily. C.D. currently takes risperidone 2 mg daily, atenolol 50 mg daily, simvastatin 40 mg daily, alprazolam 0.25 mg daily, and a baby aspirin daily. Which of the following is most appropriate course of action?
- Tell her caregiver that C.D. should experience no problems with her new medication.
 - Tell her caregiver that C.D. may be at an increased risk for developing adverse effects like nausea, headache, or restlessness due to the multiple drugs C.D. takes and ask that she report any odd behavior or new symptoms to you.
 - Contact C.D.'s doctor and recommend a different antidepressant.
 - Tell her caregiver that C.D. will probably get akathisia, an inner restlessness, and that nothing be done.
6. Which of the following is not a risk factor for developing selective serotonin reuptake inhibitor (SSRI)-induced akathisia?
- Use of multiple drugs including neuroleptics and SSRIs.
 - Previous brain trauma.
 - Age older than 30 years.
 - A large increase in dosage of an SSRI.
7. Which of the following drug classes is not a good recommendation for a patient with fluoxetine-induced akathisia?
- Centrally-acting beta-blocker
 - Peripherally acting beta-2 antagonist
 - Anticholinergic
 - Benzodiazepine
8. Which of the following is true regarding akathisia?
- It can prompt suicidal ideation.
 - It is easy to recognize.
 - It will never go away once a patient develops it.
 - SSRIs are the only drugs that cause it.
9. Which of the following drugs is not known to cause akathisia?
- Citalopram
 - Loratadine
 - Metoclopramide
 - Haloperidol
10. What is the proposed etiology of akathisia?
- Deficiency of serotonin in the brain.
 - Excess dopamine in the periphery.
 - Deficiency of dopamine in the brain.
 - Excess serotonin in the gut.

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Measure with care

A mother shared an experience she had after picking up an antibiotic liquid at her pharmacy for her 2-year-old child. After speaking with the pharmacist about the medication, the mother looked around the pharmacy for a measuring device to accurately measure the 5 mL dose.

Unable to find one, she asked the staff for help. A pharmacist located a 1-mL and a 20-mL syringe and gave her the 20-mL syringe, which was marked in 1-mL increments. However, when the mother later tried to administer the medication, she discovered that the barrel of the syringe was too large to fit into the antibiotic bottle. She considered several options: (1) using a dose cup provided with another product, (2) delaying starting the antibiotic until the next day when she could get a new device, or (3) using a kitchen teaspoon. Fortunately, this mother was able to figure out a way to accurately measure each dose, but not all patients or caregivers could do so.

In this case, the pharmacist intended to assist his patient by providing a measuring device; however, he incorrectly assumed that the caregiver would know how to use the device properly.

Pharmacists' responsibilities

In addition to providing patients with appropriate devices for measuring doses, practitioners must ensure that the patient or caregiver understands how to properly use the device with the medication. This goal is best achieved with education and a demonstration performed by the practitioner followed by a return demonstration by the user. If this technique had been used in this case, the problems or hazards encountered by the user would likely have been discovered and corrected before she left the pharmacy.

Ensure that oral syringes (without caps) or other appropriate measuring

devices are readily available for distribution or purchase at your practice site. Verify that the dosage can be accurately measured using the oral syringe. It may be necessary to keep a few different sizes on hand to ensure proper measurement of smaller doses. Coach patients on how to use these devices and ask patients to demonstrate their understanding of the instruction.

Provide education to patients and caregivers regarding the proper use of an oral syringe or other measuring device. Demonstrate how to measure and administer the dose and inform them about how to clean the device, if it is to be reused.

Time for a change to metric

Health professionals should be concerned about the number of mix-ups reported to the Institute for Safe Medication Practices involving expressions of volume—specifically confusion between milliliter and teaspoonful. When these errors appear on pharmacy-generated labels, patients receive fivefold overdoses or underdoses if undetected. In one patient report, a pharmacist labeled a prescription for azithromycin suspension with the directions to give “2 1/2 teaspoonful daily” (equivalent to 12.5 mL) instead of 2.5 mL daily. The entire contents of the bottle was administered according to the labeled instructions, and the child developed diarrhea.

In another reported error, an 8-month-old child was dispensed ranitidine syrup to treat gastroesophageal reflux disease. The pharmacy label incorrectly instructed the parent to administer “0.5 teaspoonful three times daily” (equivalent to 2.5 mL) instead of 0.5 mL three times daily. The overdose was

administered for 2 weeks and the child experienced tremors, excessive blinking, and the inability to sleep. These reactions resolved after the medication was discontinued. Similar mix-ups between teaspoonful and mL have also involved drugs such as amoxicillin, amoxicillin/clavulanic acid, fluoxetine, citalopram, and fluconazole. The figure shows an example of a dose entered as “teaspoon-



ful” instead of “mL” even though the prescriber wrote “mL.”

To prevent the teaspoonful–mL confusion, volume expression on prescriptions and pharmacy labels must be standardized. Doses for oral liquids should be expressed only in metric weights and volumes (i.e., mg and mL). This method will also eliminate potential confusion between teaspoonful and tablespoonful.

Prescribers should include the calculated dose by metric weight, not just the metric volume; the use of teaspoonful and tablespoonful should be avoided. Remove nonmetric volume expressions such as teaspoon from computer systems. Also remove any mnemonics or defaults used to generate prescriptions and labels. Double-check the directions that appear on the pharmacy label against the original prescription. Take steps to ensure that patients have an appropriate device to measure volume in milliliters when a prescription for an oral liquid medication is dispensed.

—Institute for Safe Medication Practices

The reports described in this column were received through the ISMP Medication Errors Reporting Program (MERP). Errors, close calls, or hazardous conditions may be reported on the Institute for Safe Medication Practices (www.ismp.org) website or communicated directly to ISMP by calling 800-FAIL-SAF (800-324-5723) or e-mailing ismpinfo@ismp.org. The topics in this column are covered in greater detail in *Medication Errors, 2nd edition*, written by ISMP President Michael R. Cohen, BPharm, MS, ScD. The book may be purchased from APhA at www.pharmacist.com or by calling 800-878-0729.



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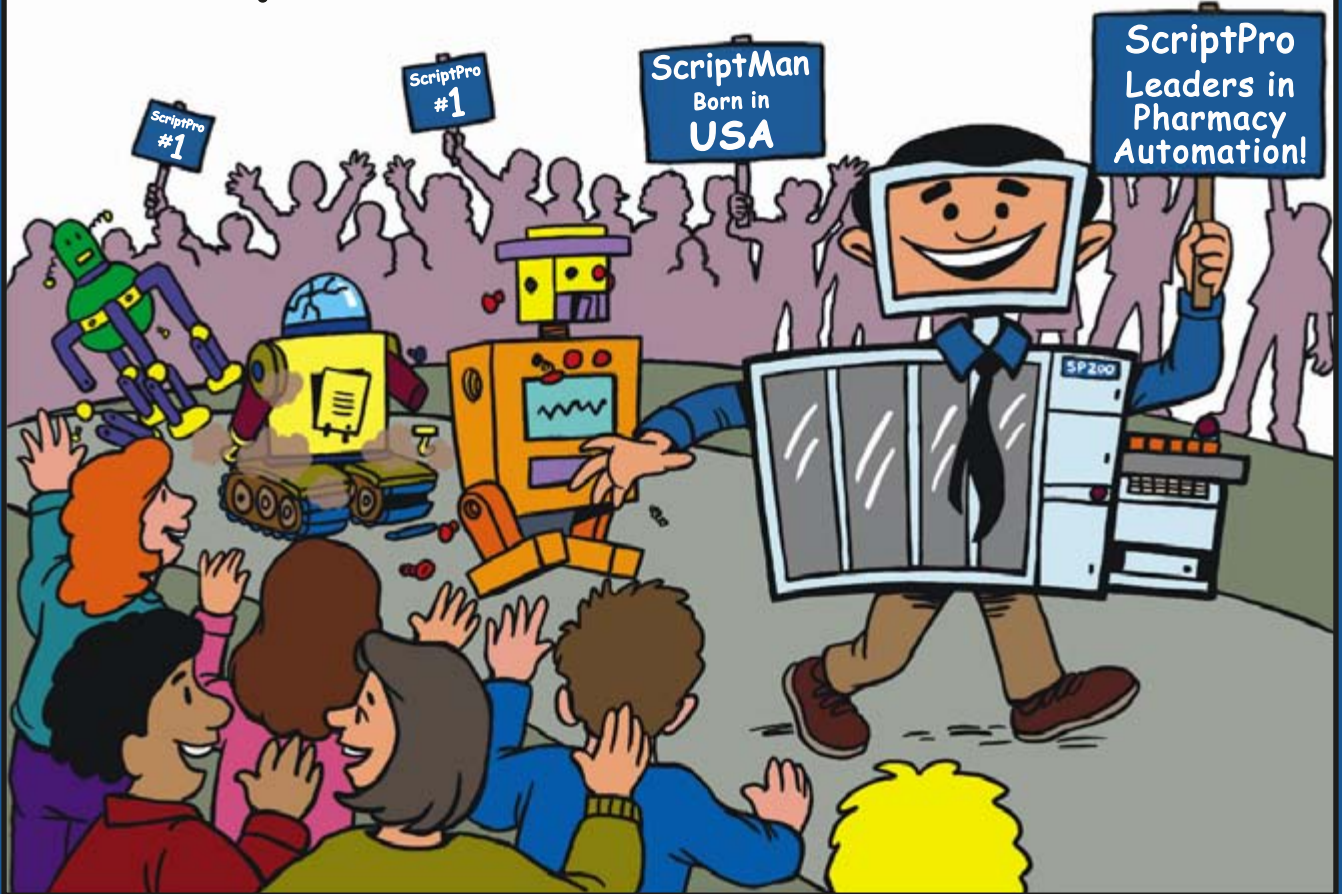
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