

# Idiopathic Granulomatous Mastitis

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## PRACTICE POINTS

- Idiopathic granulomatous mastitis (IGM) is a painful and scarring rare granulomatous breast disorder that can have a prolonged time to diagnosis that delays proper treatment.
- The pathogenesis of IGM remains poorly understood. The temporal association of the disorder with breastfeeding suggests that hyperprolactinemia or an immune response to local lobular secretions might play a role.
- Although many cases of IGM resolve without treatment, more severe cases can persist for a long period before adequate symptomatic treatment is provided with methotrexate, corticosteroids, or surgical excision.
- Before any of these therapies are applied, however, contributing factors, such as long-term breastfeeding and drugs that induce hyperprolactinemia, should be identified and withdrawn.

Idiopathic granulomatous mastitis (IGM) is a rare, poorly understood condition that presents as inflammatory nodules of the breast. It is often initially misdiagnosed as furunculosis or cellulitis. Despite the painful, scarring, and debilitating nature of the disease, patients often have a delay in accurate diagnosis and treatment. Even when IGM is considered as a diagnosis, it is one of exclusion, with the differential diagnosis including serious conditions such as breast cancer, sarcoidosis, and cutaneous tuberculosis. Therefore, appropriate workup is important. Given that IGM is a disease of the skin, it is important for dermatologists to be familiar with its presentation. We describe 3 cases of young women with this condition and demonstrate that identification of triggers or methotrexate treatment is highly successful in sparing patients the drastic surgical alternative of mastectomy. *Cutis*. 2019;103:38-42.

Idiopathic granulomatous mastitis (IGM) is rare during pregnancy; it typically is seen in women of childbearing potential from 6 months to 6 years postpartum.<sup>1</sup> Because of a temporal association with breastfeeding, it is believed

that hyperprolactinemia<sup>2</sup> or an immune response to local lobular secretions might play a role in pathogenesis. Early misdiagnosis as bacterial mastitis is common, prompting multiple antibiotic regimens. When antibiotics fail, patients are worked up for inflammatory breast cancer, given the nonhealing breast nodules. Mammography, ultrasonography, and fine-needle aspiration often are unable to rule out carcinoma, warranting excisional biopsies of nodules. The patient is then referred to rheumatology for potential sarcoidosis or to dermatology for IGM. In either case, the workup should be similar, but additional history focused on behavior and medications is essential in suspected IGM, given the association with hyperprolactinemia.

Because IGM is rare, there are no randomized, placebo-controlled trials of treatment efficacy. In many cases, patients undergo complete mastectomy, which is curative but may be psychologically and physically impactful in young women. In some cases, high-dose corticosteroids have been successful; however, because the IGM process can last longer than 2 years, patients treated in this manner are exposed to steroid morbidities.<sup>1</sup>

We report 3 cases of IGM that add to the literature on possible contributing factors, clinical presentations, and treatments for this disease. We also demonstrate that appropriate trigger identification and steroid-sparing agents, specifically methotrexate, can be breast-saving as they can alleviate this debilitating condition, obviating the need for radical surgical intervention.

## CASE REPORTS

### Patient 1

A 40-year-old woman with a 4-year history of breastfeeding noted a grape-sized nodule on the left breast that grew to the size of a grapefruit after 2 weeks. Ulceration and drainage periodically occurred, forming pink plaques along the lateral aspects of the breast after healing. Her primary care provider suspected infectious mastitis; she was given an oral antibiotic (cephalexin) and intravenous antibiotics without improvement.

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The eTable is available in the Appendix online at [www.mdedge.com/cutis](http://www.mdedge.com/cutis).

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**Imaging**—Subsequent magnetic resonance imaging revealed a large, irregular, enhancing mass within the outer left breast (6.5 cm at greatest dimension) with additional surrounding amorphous enhancement highly suspicious for malignancy. There also were multiple prominent left axillary lymph nodes, with the largest demonstrating a cortical thickness of 8 mm.

**Biopsy**—Core breast biopsy showed benign tissue with fat necrosis. Fine-needle aspiration revealed few benign ductal cells and rare histiocytes; because these findings were nondiagnostic and cancer was still a consideration, the patient underwent excisional biopsy.

Histologic sections of breast tissue showed extensive lobulocentric inflammation comprising histiocytes and lymphocytes, with neutrophils admixed and forming microabscesses (Figure 1A). Multinucleated giant cells and single-cell necrosis were seen, but true caseous necrosis was absent (Figure 1B). Duct spaces often contained inflammatory cells or secretions. Special stains for fungal and acid-fast bacterial microorganisms were negative.

**Referral to Dermatology**—Granulomatous lobular mastitis was diagnosed, and the patient was referred to dermatology. On presentation to dermatology, the left breast showed a 6-cm area of firm induration and overlying

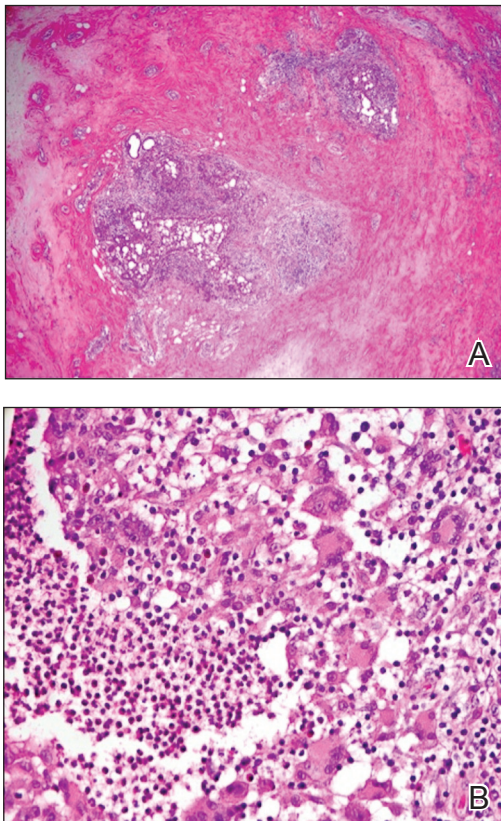
peau d'orange change to the epidermis (Figure 2A). Based on pathologic analysis, she was worked up for a possible granulomatous etiology. Negative purified protein derivative (tuberculin)(PPD) and a normal chest radiograph ruled out tuberculosis. Normal chest radiography, serum Ca<sup>2+</sup> and angiotensin-converting enzyme (ACE) levels, and ophthalmology examination ruled out sarcoidosis.

The patient reported she continued breastfeeding her 4-year-old son. Additionally, she had been started on trazadone and buspirone for alcohol abuse recovery, then switched to and maintained on fluoxetine 1 year before developing these symptoms.

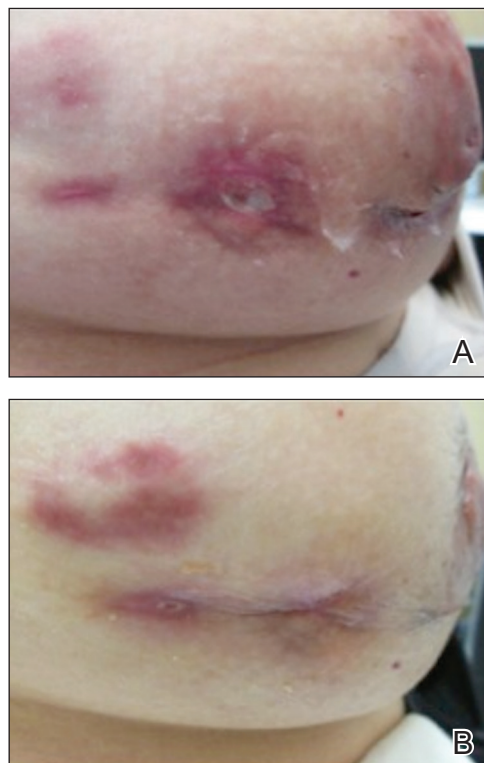
Buspirone, fluoxetine, and prolonged breastfeeding all contribute to hyperprolactinemia, a possible trigger of IGM. The patient was therefore advised to stop breastfeeding and to be switched from fluoxetine to a medication that would not increase the prolactin level. She did not require methotrexate treatment because her condition resolved rapidly after breastfeeding and fluoxetine were discontinued (Figure 2B).

**Patient 2**

A 40-year-old woman with no history of breastfeeding who gave birth 4.5 years prior presented to her primary care provider with a painful breast lump and rash on the right breast of 2 months' duration. Infectious mastitis was



**FIGURE 1.** A, Histopathology showed breast tissue with inflammation in a lobulocentric distribution (H&E, original magnification ×40). B, Neutrophilic microabscess (left side) and multinucleated cells also were seen (H&E, original magnification ×400).



**FIGURE 2.** A, Firm induration and overlying peau d'orange change to the epidermis at presentation to the dermatology department. B, Resolution after discontinuation of breastfeeding and fluoxetine.

suspected; she was given cephalexin and clindamycin without improvement of symptoms.

**Imaging**—Mammography and ultrasonography were nondiagnostic.

**Biopsy**—Breast biopsy showed tissue with large expanses of histiocytes, neutrophils, lymphocytes, plasma cells, and multinucleated giant cells (Figure 3A). Many discrete granulomas were seen against this mixed inflammatory background, associated with focal fat necrosis (Figure 3B). Special stains were negative for microorganisms. Histologic findings were consistent with granulomatous mastitis.

**Referral to Dermatology**—On presentation to dermatology, the patient was worked up for a possible granulomatous etiology, which included a negative PPD, as well as a normal chest radiograph, serum Ca<sup>2+</sup> and ACE levels, and ophthalmology examination. Review of symptoms (ROS), medical history, and medication review were unremarkable.

By exclusion, the patient was given a diagnosis of IGM and started on methotrexate (15 mg weekly) with folic acid (1 mg daily). The condition of the right breast improved within 4 weeks of starting methotrexate; however, methotrexate was increased to 30 mg weekly because of occasional flares. The patient remained on methotrexate without further IGM flares for

8 months compared to prior unremitting pain and drainage. She was then tapered from methotrexate over 6 weeks without additional flares.

**Patient 3**

A 27-year-old woman who gave birth 2 years prior and discontinued breastfeeding 6 weeks after delivery noted bilateral breast rashes for several months. The lesions were growing in size, tender, and draining. Her primary care provider suspected infectious mastitis and prescribed antibiotics, which were ineffective.

**Biopsy**—Breast core biopsy showed histologic findings similar to patients 1 and 2, including lobulocentric mixed inflammation, neutrophilic microabscesses, and scattered discrete granulomas. Microorganisms were not found using special stains. Breast cancer was ruled out, and granulomatous mastitis was diagnosed.

**Referral to Dermatology**—Two years earlier, the patient tested positive for latent tuberculosis and was prescribed a 9-month regimen of isoniazid. At the current presentation, she did not have symptoms of active tuberculosis on ROS (ie, no cough, hemoptysis, weight loss, night sweats); a chest radiograph was normal. Additionally, serum Ca<sup>2+</sup> and ACE levels as well as an ophthalmology examination were normal, and she was not taking any medications known to increase the prolactin level.

The patient was started on methotrexate (12.5 mg weekly) and folic acid (1 mg daily). She had 1 IGM flare and was given a tapering regimen of prednisone. She received methotrexate for 14 months, tapered during the final 3 months. She has been off methotrexate for 3 years without IGM flares and appears to be in complete remission.

**COMMENT**

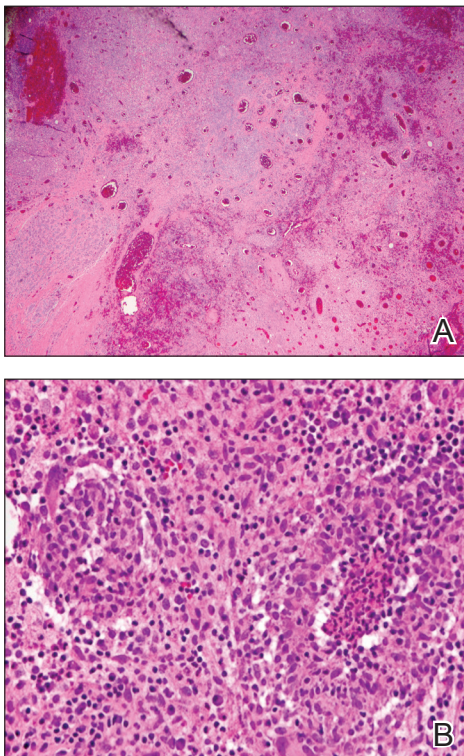
We report 3 cases of IGM, which contribute to the literature on possible presentations, causes, and conservative treatment of this rare connective-tissue disorder.

**Differential Diagnosis**

The time between recognition of symptoms and diagnosis and treatment of IGM often is prolonged because IGM can present similarly to other disorders, such as infection, breast cancer, tuberculosis, and sarcoidosis. Idiopathic granulomatous mastitis is a diagnosis of exclusion, made after obtaining evidence of granulomatous inflammation on breast biopsy and ruling out other granulomatous disorders, such as tuberculosis and sarcoidosis (Table 1).<sup>3,4</sup>

**Tuberculosis**—A full ROS and a PPD test or T-SPOT.TB test can be helpful in ruling out tuberculosis; because anergy occurs in some patients, tuberculosis should be evaluated in the context of known immunosuppression or human immunodeficiency virus status, or in the case of miliary tuberculosis.

Chest radiography findings classically showing upper lobe infiltrates with cavities in active tuberculosis also should be sought.<sup>3</sup> Ziehl-Neelsen staining of 2 sputum specimens, assessed by conventional light microscopy



**FIGURE 3.** A, Large expanses of histiocytes, neutrophils, lymphocytes, plasma cells, and multinucleated giant cells were seen (H&E, original magnification ×20). B, Two granulomas were seen in a mixed inflammatory background; the granuloma on the right side contained a neutrophilic microabscess (H&E, original magnification ×400).



at the time of tissue biopsy has 64% sensitivity and 98% specificity for detecting *Mycobacterium tuberculosis*; auramine O staining, examined with light-emitting diode fluorescence microscopy, has 73% sensitivity and 93% specificity.<sup>5</sup>

**Sarcoidosis**—Because more than 90% of sarcoid patients have lung disease, a chest radiograph is used to screen for hilar lymphadenopathy.<sup>3</sup> An elevated serum ACE level also can be helpful in diagnosis, but patients do not always have increased ACE, which can occur in other diseases, such as hyperthyroidism and miliary tuberculosis. Sarcoid granulomas can increase active vitamin D production, which in turn increases serum Ca<sup>2+</sup> in 10% of sarcoid patients. Last, an ophthalmology evaluation should be obtained to rule out anterior or posterior uveitis that can occur in sarcoidosis and initially remain asymptomatic.<sup>3</sup> Once these other causes of granulomatous inflammation have been ruled out, a diagnosis of IGM can be made.

**Prolactinoma**—Prolactinoma is an important cause of hyperprolactinemia that can be screened for based on ROS and the serum prolactin level. Prolactinoma can

cause oligomenorrhea or amenorrhea and galactorrhea in 90% and 80% of premenopausal women, respectively, as well as erectile dysfunction and decreased libido in men. Infertility, headache, and visual impairment may be experienced in both sexes.<sup>4</sup>

A normal prolactin level is less than 25 µg/L; more than 25 µg/L but less than 100 µg/L usually is due to certain drugs (eTable),<sup>6-11</sup> estrogen, or idiopathic reasons; and more than 150 µg/L usually is due to prolactinoma.<sup>5</sup> In many cases, removal of hyperprolactinemia-precipitating factors can resolve disease, as in patient 1. If symptoms continue or precipitating factors are absent, IGM symptom-based treatment should be administered.

**Course and Management**

Idiopathic granulomatous mastitis is self-limited and usually resolves within 2 years. Therefore, the goal of treatment is to suppress associated pain and drainage until the active inflammatory phase of IGM self-resolves. An established protocol for treating IGM does not exist, but common treatments include corticosteroids, methotrexate, and limited or

**TABLE 1. Workup of Granulomatous Breast Disease<sup>3</sup>**

Diagnosis	Tests
Behaviors associated with IGM	Long-term breastfeeding
Medications associated with IGM	See eTable
Prolactinoma <sup>4</sup>	MRI evidence of pituitary adenoma, serum prolactin level (>150 µg/L)
Sarcoidosis	ACE, chest radiograph, ophthalmology examination (for uveitis), serum Ca <sup>2+</sup>
Triggering infection ( <i>Corynebacterium</i> , <i>Histoplasma</i> , mycoses)	Tissue culture for bacteria, fungi, atypical mycobacteria
Tuberculosis	PPD, T-SPOT.TB test, tissue staining

Abbreviations: IGM, idiopathic granulomatous mastitis; MRI, magnetic resonance imaging; ACE, angiotensin-converting enzyme; PPD, purified protein derivative (tuberculin).

**TABLE 2. Treatment Options for Idiopathic Granulomatous Mastitis<sup>12-16</sup>**

Treatment	Symptom Resolution	Recurrence	Side Effects	Level of Evidence
Corticosteroids	80%	23%	Cushing syndrome, gastritis, glucose intolerance, osteoporosis, weight gain	Prospective observational studies
Methotrexate (with folic acid)	83%	17%	Birth defects, <sup>a</sup> stomatitis	Case reports
Surgical excision	100%	5%–50%	Abscess, chronic pyogenic secretions, disfigurement, fistula	Prospective and retrospective observational studies

<sup>a</sup>When taken during pregnancy.

wide surgical excision (Table 2).<sup>12-16</sup> Before beginning any of these treatments, IGM triggers, such as breastfeeding and drugs that induce hyperprolactinemia, should be removed.

It is important to consider which treatment option is best for limiting disease recurrence and adverse effects (AEs). Keep in mind that the available data are limited, as there are no randomized controlled trials looking at these treatments. Nevertheless, we recommend methotrexate as first line because it resolves granulomatous inflammation symptoms without invasive surgery, while limiting corticosteroid AEs.<sup>12</sup>

With or without concurrent use of corticosteroids, surgical excision typically is the mainstay of treatment. However, surgical excision of IGM lesions can be complicated by abscess formation, fistula, and chronic pyogenic secretions, in addition to a 5% to 50% rate of recurrence of disease.<sup>12-14</sup> Limited excision often is insufficient; therefore, wide local excision, in which negative margins around granulomatous inflammation are obtained, is the surgical modality of choice.<sup>14</sup> Wide local excision can be disfiguring to the breast in young women affected by IGM, making it an undesirable treatment option.

Corticosteroids often have been used to treat IGM, but their efficacy is variable, symptoms can recur upon drug removal, and remarkable AEs can result from long-term use.<sup>12</sup> Additionally, corticosteroid therapy often is used in combination with excision, making it difficult to determine the extent to which corticosteroids or excision are more beneficial. In a prospective observational study, corticosteroid therapy alone resolved 80% of IGM symptoms after 159 days on average. After complete symptom resolution, 23% of patients had disease recurrence.<sup>9</sup> Observed AEs included gastritis, weight gain, osteoporosis, glucose intolerance, and Cushing syndrome.<sup>12,15</sup>

Methotrexate for IGM has not been reviewed in a randomized controlled trial; case reports have shown 83% symptom resolution, with 17% recurrence and limited long-term AEs.<sup>12</sup> Because the active phase of IGM can persist for 2 years, immunosuppressive therapy with limited AEs is necessary. Many AEs can occur when high-dose methotrexate is given for cancer treatment. Low-dose methotrexate has been extensively studied in long-term treatment of rheumatoid arthritis. Adverse effects may include gastrointestinal tract upset and hepatic dysfunction, which are limited when given with folic acid.

Regardless of folic acid cotreatment, stomatitis may occur. Women should use an effective method of birth control because severe birth defects may occur on even low-dose methotrexate.<sup>16</sup>

Compared to corticosteroid or surgical treatment, we recommend low-dose methotrexate therapy based on its high efficacy with limited AEs. An occasional mild flare of IGM symptoms with methotrexate is not unusual. If it occurs, corticosteroids can be added and tapered for as long as 2 weeks to speed up resolution of flares while reducing long-term AEs of corticosteroids.

Surgical excision can be performed in cases refractory to all systemic therapies.

## CONCLUSION

Idiopathic granulomatous mastitis is a rare granulomatous breast disorder that can have a prolonged time to diagnosis, delaying proper treatment. Many cases self-resolve, but more severe cases can persist for a long period before adequate symptomatic treatment is achieved by methotrexate, corticosteroids, or surgical excision. Before using these therapies, it is important to identify and remove contributing factors, such as long-term breastfeeding and drugs that induce hyperprolactinemia. Improving the rate of IGM diagnosis and treatment would greatly benefit these patients. We report 1 case in which removal of possible precipitating IGM factors led to symptom resolution and 2 cases in which methotrexate was an effective IGM treatment that limited the need for invasive procedures and corticosteroid AEs.

## REFERENCES

1. Patel RA, Strickland P, Sankara IR, et al. Idiopathic granulomatous mastitis: case reports and review of literature. *J Gen Intern Med.* 2010;25:270-273.
2. Bellavia M, Damiano G, Palumbo VD, et al. Granulomatous mastitis during chronic antidepressant therapy: is it possible a conservative therapeutic approach? *J Breast Cancer.* 2012;15:371-372.
3. Longo D, Fauci A, Kasper D, et al. *Harrison's Principles of Internal Medicine.* 18th ed. New York, NY: McGraw-Hill; 2012.
4. Davis JL, Cattamanchi A, Cuevas LE, et al. Diagnostic accuracy of same-day microscopy versus standard microscopy for pulmonary tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis.* 2013;13:147-154.
5. Casanueva FF, Molitch ME, Schlechte JA, et al. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. *Clin Endocrinol (Oxf).* 2006;65:265-273.
6. Akbulut S, Arikanoğlu Z, Senol A, et al. Is methotrexate an acceptable treatment in the management of idiopathic granulomatous mastitis? *Arch Gynecol Obstet.* 2011;284:1189-1195.
7. Bani-Hani KE, Yaghan RJ, Matala II, et al. Idiopathic granulomatous mastitis: time to avoid unnecessary mastectomies. *Breast J.* 2004;10:318-322.
8. Asoğlu O, Özmen V, Karanlık H, et al. Feasibility of surgical management in patients with granulomatous mastitis. *Breast J.* 2005;11:108-114.
9. Pandey TS, Mackinnon JC, Bressler L, et al. Idiopathic granulomatous mastitis—a prospective study of 49 women and treatment outcomes with steroid therapy. *Breast J.* 2014;20:258-266.
10. Shea B, Swinden MV, Tanjong Ghogomu E, et al. Folic acid and folic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. *Cochrane Database Syst Rev.* 2013;5:CD000951.
11. Molitch ME. Drugs and prolactin. *Pituitary.* 2008;11:209-218.
12. Peuskens J, Pani L, Detraux J, et al. The effects of novel and newly approved antipsychotics on serum prolactin levels: a comprehensive review. *CNS Drugs.* 2014;28:421-453.
13. Kondo T, Otani K, Ishida M, et al. Adverse effects of zotepine and their relationship to serum concentrations of the drug and prolactin. *Ther Drug Monit.* 1994;16:120-124.
14. Sharpe M, Clements A, Hawton K, et al. Increased prolactin response to buspirone in chronic fatigue syndrome. *J Affect Disord.* 1996;41:71-76.
15. Risch SC, Janowsky DS, Siever LJ, et al. Correlated cholinomimetic-stimulated beta-endorphin and prolactin release in humans. *Peptides.* 1982;3:319-322.
16. Pedrini JL, Francalacci Savaris R, Casales Schorr M, et al. The effect of neoadjuvant chemotherapy on hormone receptor status, HER2/neu and prolactin in breast cancer. *Tumori.* 2011;97:704-710.

APPENDIX

**eTABLE. Drugs That Induce Sustained Hyperprolactinemia<sup>6,7</sup>**

Class	Medications
Antihypertensives	Labetalol, methyldopa, reserpine, verapamil
Antipsychotics	Typical: butyrophenones (eg, haloperidol), phenothiazines (eg, chlorpromazine, thioridazine), thioxanthenes; atypical: asenapine, benzamides (eg, amisulpride), clozapine, iloperidone, lurasidone, molindone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, zotepine <sup>8</sup>
Hormone-based preparations	Antiandrogens, estrogens, oral contraceptives
Monoamine oxidase inhibitor antidepressants	Clorgyline, pargyline, tranylcypromine
Opiates and cocaine	Cocaine, methadone, morphine
Selective serotonin-reuptake inhibitor antidepressants	Citalopram, fluoxetine, fluvoxamine, paroxetine
Tricyclic antidepressants	Amitriptyline, amoxapine, clomipramine, desipramine, imipramine, maprotiline
Other psychotropics	Alprazolam, buspirone <sup>9</sup>
Others	Alcohol, chemotherapeutic agents, <sup>11</sup> fenfluramine, physostigmine <sup>10</sup>