28 - 29.28 Selective Serotonin Reuptake Inhibitors

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it helped ameliorate the long-standing stigma of depression and its treatment. Fluoxetine was followed by other SSRIs. These include sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), citalopram (Celexa), escitalopram (Lexapro), and vilazodone (Viibryd). These drugs are all equally effective in treating depression but some are approved by the U.S. Food and Drug Administration (FDA) for multiple indications, such as major depression, obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), premenstrual dysphoric disorder (PMDD), panic disorder, and social phobia (social anxiety disorder) (Table 29.28-1). Note that fluvoxamine is not FDA approved as an antidepressant, a fact that is due to a marketing decision. It is considered an antidepressant in other countries. Table 29.28-1 Currently Approved Indications of the Selective Serotonin Reuptake Inhibitors in the United States for Adult and Pediatric Populations

Although all SSRIs are equally effective, there are meaningful differences in pharmacodynamics, pharmacokinetics, and side effects, differences that might affect clinical responses among individual patients. This would explain why some patients have better clinical responses to a particular SSRI than another. The SSRIs have proven more problematic in terms of some side effects than the original clinical trials suggested. Quality-of-life–associated adverse effects such as nausea, sexual dysfunction, and weight gain sometimes mitigate the therapeutic benefits of the SSRIs. There can also be distressing withdrawal symptoms when SSRIs are stopped abruptly. This is especially true with paroxetine, but also occurs when other SSRIs with short half-lives are stopped. PHARMACOLOGICAL ACTIONS Pharmacokinetics A significant difference among the SSRIs is their broad range of serum half-lives. Fluoxetine has the longest half-life: 4 to 6 days; its active metabolite has a half-life of 7 to 9 days. The half-life of sertraline is 26 hours, and its less active metabolite has a halflife of 3 to 5 days. The half-lives of the other three, which do not have metabolites with significant pharmacological activity, are 35 hours for citalopram, 27 to 32 hours for escitalopram, 21 hours for paroxetine, and 15 hours for fluvoxamine. As a rule, the SSRIs are well absorbed after oral administration and have their peak effects in the range of 3 to 8 hours. Absorption of sertraline may be slightly enhanced by food. There are also differences in plasma protein–binding percentages among the SSRIs, with sertraline, fluoxetine, and paroxetine being the most highly bound and escitalopram being the least bound. All SSRIs are metabolized in the liver by the CYP450 enzymes. Because the SSRIs have such a wide therapeutic index, it is rare that other drugs produce problematic increases in SSRI concentrations. The most important drug–drug interactions involving the SSRIs occur as a result of the SSRIs inhibiting the metabolism of the coadministered medication. Each of the SSRIs possesses a potential for slowing or blocking the metabolism of many drugs (Table 29.28-2). Fluvoxamine is the most problematic of the

drugs in this respect. It has a marked effect on several of the CYP enzymes. Examples of clinically significant interactions include fluvoxamine and theophylline (Slo-Bid, TheoDur) through CYP1A2 interaction; fluvoxamine and clozapine (Clozaril) through CYP1A2 inhibition; and fluvoxamine with alprazolam (Xanax) or clonazepam (Klonopin) through CYP3A4 inhibition. Fluoxetine and paroxetine also possess significant effects on the CYP2D6 isozyme, which may interfere with the efficacy of opiate analogs, such as codeine and hydrocodone, by blocking the conversion of these agents to their active form. Thus, coadministration of fluoxetine and paroxetine with an opiate interferes with its analgesic effects. Sertraline, citalopram, and escitalopram are least likely to complicate treatment because of interactions. Table 29.28-2 CYP450 Inhibitory Potential of Commonly Prescribed Antidepressants The pharmacokinetics of vilazodone (5 to 80 mg) are dose proportional. Steady-state plasma levels are achieved in about 3 days. Elimination of vilazodone is primarily by

hepatic metabolism with a terminal half-life of approximately 25 hours. Pharmacodynamics The SSRIs are believed to exert their therapeutic effects through serotonin reuptake inhibition. They derive their name because they have little effect on reuptake of norepinephrine or dopamine. Often, adequate clinical activity and saturation of the 5HT transporters are achieved at starting dosages. As a rule, higher dosages do not increase antidepressant efficacy but may increase the risk of adverse effects. Citalopram and escitalopram are the most selective inhibitors of serotonin reuptake, with very little inhibition of norepinephrine or dopamine reuptake and very low affinities for histamine H1, γ-aminobutyric acid (GABA), or benzodiazepine receptors. The other SSRIs have a similar profile except that fluoxetine weakly inhibits norepinephrine reuptake and binds to 5-HT2C receptors, sertraline weakly inhibits norepinephrine and dopamine reuptake, and paroxetine has significant anticholinergic

activity at higher dosages and binds to nitric oxide synthase. The SSRI vilazodone has 5HT1A receptor agonist properties. The clinical implications of the 5-HT1A receptor agonist effects are not yet evident. A pharmacodynamic interaction appears to underlie the antidepressant effects of combined fluoxetine–olanzapine. When taken together, these drugs increase brain concentrations of norepinephrine. Concomitant use of SSRIs and drugs in the triptan class (sumatriptan [Imitrex], naratriptan [Amerge], rizatriptan [Maxalt], and zolmitriptan [Zomig]) may result in a serious pharmacodynamic interaction—the development of a serotonin syndrome (see “Precautions and Adverse Reactions”). However, many people use triptans while taking low doses of an SSRI for headache prophylaxis without adverse reaction. A similar reaction may occur when SSRIs are combined with tramadol (Ultram). THERAPEUTIC INDICATIONS Depression In the United States, all SSRIs other than fluvoxamine have been approved by the FDA for treatment of depression. Several studies have found that antidepressants with serotonin-norepinephrine activity—drugs such as the MAOIs, TCAs, venlafaxine (Effexor), and mirtazapine (Remeron)—may produce higher rates of remission than SSRIs in head-to-head studies. The continued role of SSRIs as first-line treatment thus reflects their simplicity of use, safety, and broad spectrum of action. Direct comparisons of individual SSRIs have not revealed any to be consistently superior to another. There nevertheless can be considerable diversity in response to the various SSRIs among individuals. For example, more than 50 percent of people who respond poorly to one SSRI will respond favorably to another. Thus, before shifting to non-SSRI antidepressants, it is most reasonable to try other agents in the SSRI class for persons who did not respond to the first SSRI. Some clinicians have attempted to select a particular SSRI for a specific person on the basis of the drug’s unique adverse effect profile. For example, thinking that fluoxetine is an activating and stimulating SSRI, they may assume it is a better choice for an abulic person than paroxetine, which is presumed to be a sedating SSRI. These differences, however, usually vary from person to person. Analyses of clinical trial data show that the SSRIs are more effective in patients with more severe symptoms of major depression than those with milder symptoms. Suicide. The FDA has issued a black box warning for antidepressants and suicidal thoughts and behavior in children and young adults. This warning is based on a decadeold analysis of clinical trial data. More recent, comprehensive reanalysis of data has shown that suicidal thoughts and behavior decreased over time for adult and geriatric patients treated with antidepressants as compared with placebo. No differences were found for youths. In adults, reduction in suicide ideation and attempts occurred through a reduction in depressive symptoms. In all age groups, severity of depression improved

with medication and was significantly related to suicide ideation or behavior. It appears that SSRIs, as well as serotonin-norepinephrine reuptake inhibitors (SNRIs), have a protective effect against suicide that is mediated by decreases in depressive symptoms with treatment. For youths, no significant effects of treatment on suicidal thoughts and behavior were found, although depression responded to treatment. No evidence of increased suicide risk was observed in youths receiving active medication. It is important to keep in mind that SSRIs, like all antidepressants, prevent potential suicides as a result of their primary action, the shortening and prevention of depressive episodes. In clinical practice, a few patients become especially anxious and agitated when started on an SSRI. The appearance of these symptoms could conceivably provoke or aggravate suicidal ideation. Thus, all depressed patients should be closely monitored during the period of maximum risk, the first few days and weeks they are taking SSRIs. Depression During Pregnancy and Postpartum. Rates of relapse of major depression during pregnancy among women who discontinue, attempt to discontinue, or modify their antidepressant regimens are extremely high. Rates range from 68 to 100 percent of patients. Thus, many women need to continue taking their medication during pregnancy and postpartum. The impact of maternal depression on infant development is unknown. There is no increased risk for major congenital malformations after exposure to SSRIs during pregnancy. Thus, the risk of relapse into depression when a newly pregnant mother is taken off SSRIs is several-fold higher than the risk to the fetus of exposure to SSRIs. There is some evidence suggesting increased rates of special care nursery admissions after delivery for children of mothers taking SSRIs. There is also a potential for a discontinuation syndrome with paroxetine. However, there is an absence of clinically significant neonatal complications associated with SSRI use. Studies that have followed children into their early school years have failed to find any perinatal complications, congenital fetal anomalies, decreases in global intelligence quotient (IQ), language delays, or specific behavioral problems attributable to the use of fluoxetine during pregnancy. Postpartum depression (with or without psychotic features) affects a small percentage of mothers. Some clinicians start administering SSRIs if the postpartum blues extend beyond a few weeks or if a woman becomes depressed during pregnancy. The head start afforded by starting SSRI administration during pregnancy if a woman is at risk for postpartum depression also protects the newborn, toward whom the woman may have harmful thoughts after parturition. Babies whose mothers are taking an SSRI in the later part of pregnancy may be at a slight risk of developing pulmonary hypertension. Data about the risk of this side effect are inconclusive, but it is estimated to involve 1 to 2 babies for 1,000 births. Paroxetine should be avoided during pregnancy. The FDA has classified paroxetine as a pregnancy Category D medication. In 2005, the FDA issued an alert that paroxetine increases the risk of birth defects, particularly heart defects, when women take it during the first 3 months of pregnancy. Paroxetine should

usually not be taken during pregnancy, but for some women who have already been taking paroxetine, the benefits of continuing paroxetine may be greater than the potential risk to the baby. Women taking paroxetine who are pregnant, think they may be pregnant, or plan to become pregnant should talk to their physicians about the potential risks of taking paroxetine during pregnancy. The FDA alert was based on the findings of studies that showed that women who took paroxetine during the first 3 months of pregnancy were about one and a half to two times as likely to have a baby with a heart defect as women who received other antidepressants or women in the general population. Most of the heart defects in these studies were not life-threatening and happened mainly in the inside walls of the heart muscle where repairs can be made if needed

(atrial and ventricular septal defects). Sometimes these septal defects resolve without treatment. In one of the studies, the risk of heart defects in babies whose mothers had taken paroxetine early in pregnancy was 2 percent, compared with a 1 percent risk in the whole population. In the other study, the risk of heart defects in babies whose mothers had taken paroxetine in the first 3 months of pregnancy was 1.5 percent, compared with 1 percent in babies whose mothers had taken other antidepressants in the first 3 months of pregnancy. This study also showed that women who took paroxetine in the first 3 months of pregnancy were about twice as likely to have a baby with any birth defect as women who took other antidepressants. Very small amounts of SSRIs are found in breast milk and no harmful effects have been found in breastfed babies. Concentrations of sertraline and escitalopram are especially low in breast milk. However, in some cases, reported concentrations may be higher than average. No decision regarding the use of an SSRI is risk free. It is thus important to document that communication of potential risks to the patient has taken place. Depression in Elderly and Medically Ill Persons. The SSRIs are safe and well tolerated when used to treat elderly and medically ill persons. As a class, they have little or no cardiotoxic, anticholinergic, antihistaminergic, or α-adrenergic adverse effects. Paroxetine does have some anticholinergic activity, which may lead to constipation and worsening of cognition. The SSRIs can produce subtle cognitive deficits, prolonged bleeding time, and hyponatremia, all of which may impact the health of this population. The SSRIs are effective in poststroke depression and dramatically reduce the symptom of crying. Depression in Children. The use of SSRI antidepressants in children and adolescents has been controversial. Few studies have shown clear-cut benefits from the use of these drugs, and studies show that there may be an increase in suicidal or aggressive impulses. However, some children and adolescents do exhibit dramatic responses to these drugs in terms of depression and anxiety. Fluoxetine has most consistently demonstrated effectiveness in reducing symptoms of depressive disorder in both children and adolescents. This may be a function of the quality of the clinical trials involved. Sertraline has been shown to be effective in treating social anxiety disorder in

this population, especially when combined with cognitive-behavioral therapy. Given the potential negative effect of untreated depression and anxiety in a young population and the uncertainty about many aspects of how children and adolescents might react to medication, any use of SSRIs should be undertaken only within the context of comprehensive management of the patient. Anxiety Disorders Obsessive-Compulsive Disorder. Fluvoxamine, paroxetine, sertraline, and fluoxetine are indicated for treatment of OCD in persons older than the age of 18 years. Fluvoxamine and sertraline have also been approved for treatment of children with OCD (ages 6 to 17 years). About 50 percent of persons with OCD begin to show symptoms in childhood or adolescence, and more than half of these respond favorably to medication. Beneficial responses can be dramatic. Long-term data support the model of OCD as a genetically determined, lifelong condition that is best treated continuously with drugs and cognitive-behavioral therapy from the onset of symptoms in childhood throughout the lifespan. SSRI dosages for OCD may need to be higher than those required to treat depression. Although some response can be seen in the first few weeks of treatment, it may take several months for the maximum effects to become evident. Patients who fail to obtain adequate relief of their OCD symptoms with an SSRI often benefit from the addition of a small dose of risperidone (Risperdal). Apart from the extrapyramidal side effects of risperidone, patients should be monitored for increases in prolactin levels when this combination is used. Clinically, hyperprolactinemia may manifest as gynecomastia and galactorrhea (in both men and women) and loss of menses. A number of disorders are now considered to be within the

OCD spectrum. This includes a number of conditions and symptoms characterized by nonsuicidal selfmutilation, such as trichotillomania, eyebrow picking, nose picking, nail biting, compulsive picking of skin blemishes, and cutting. Patients with these behaviors benefit from treatment with SSRIs. Other spectrum disorders include compulsive gambling, compulsive shopping, hypochondriasis, and body dysmorphic disorder. Panic Disorder. Paroxetine and sertraline are indicated for treatment of panic disorder, with or without agoraphobia. These agents work less rapidly than do the benzodiazepines alprazolam and clonazepam but are far superior to the benzodiazepines for treatment of panic disorder with comorbid depression. Citalopram, fluvoxamine, and fluoxetine also may reduce spontaneous or induced panic attacks. Because fluoxetine can initially heighten anxiety symptoms, persons with panic disorder must begin taking small dosages (5 mg a day) and increase the dosage slowly. Low doses of benzodiazepines may be given to manage this side effect. Social Anxiety Disorder. SSRIs are effective agents in the treatment of social phobia. They reduce both symptoms and disability. The response rate is comparable to

that seen with the MAOI phenelzine (Nardil), the previous standard treatment. The SSRIs are safer to use than MAOIs or benzodiazepines. Posttraumatic Stress Disorder. Pharmacotherapy for PTSD must target specific symptoms in three clusters: re-experiencing, avoidance, and hyperarousal. For long-term treatment, SSRIs appear to have a broader spectrum of therapeutic effects on specific PTSD symptom clusters than do TCAs and MAOIs. Benzodiazepine augmentation is useful in the acute symptomatic state. The SSRIs are associated with marked improvement of both intrusive and avoidant symptoms. Generalized Anxiety Disorder. The SSRIs may be useful for the treatment of specific phobias, generalized anxiety disorder, and separation anxiety disorder. A thorough, individualized evaluation is the first approach, with particular attention to identifying conditions amenable to drug therapy. In addition, cognitive-behavioral or other psychotherapies can be added for greater efficacy. Bulimia Nervosa and Other Eating Disorders Fluoxetine is indicated for treatment of bulimia, which is best done in the context of psychotherapy. Dosages of 60 mg a day are significantly more effective than 20 mg a day. In several well-controlled studies, fluoxetine in dosages of 60 mg a day was superior to placebo in reducing binge eating and induced vomiting. Some experts recommend an initial course of cognitive-behavioral therapy alone. If there is no response in 3 to 6 weeks, then fluoxetine administration is added. The appropriate duration of treatment with fluoxetine and psychotherapy has not been determined. Fluvoxamine was not effective at a statistically significant level in one double-blind, placebo-controlled trial for inpatients with bulimia. Anorexia Nervosa. Fluoxetine has been used in inpatient treatment of anorexia nervosa to attempt to control comorbid mood disturbances and obsessive-compulsive symptoms. However, at least two careful studies, one of 7 months’ and one of 24 months’ duration, failed to find that fluoxetine affected the overall outcome and the maintenance of weight. Effective treatments for anorexia include cognitive-behavioral, interpersonal, psychodynamic, and family therapies in addition to a trial with SSRIs. Obesity. Fluoxetine, in combination with a behavioral program, has been shown to be only modestly beneficial for weight loss. A significant percentage of all persons who take SSRIs, including fluoxetine, lose weight initially but later may gain weight. However, all SSRIs may cause initial weight gain. Premenstrual Dysphoric Disorder. PMDD is characterized by debilitating mood and behavioral changes in the week preceding menstruation that interfere with normal functioning. Sertraline, paroxetine, fluoxetine, and fluvoxamine have been reported to

reduce the symptoms of PMDD. Controlled trials of fluoxetine and sertraline administered either throughout the cycle or only during the luteal phase (the 2-week period between ovulation and menstruation) showed both schedules to be equally effective. An additional observation of unclear significance was that fluoxetine was associated with changing the duration of the menstrual period by more than 4 days, either lengthening or shortening it. The effects of SSRIs on menstrual cycle length are mostly unknown and may warrant careful monitoring in women of reproductive age.

Off-Label Uses Premature Ejaculation. The antiorgasmic effects of SSRIs make them useful as a treatment for men with premature ejaculation. The SSRIs permit intercourse for a significantly longer period and are reported to improve sexual satisfaction in couples in which the man has premature ejaculation. Fluoxetine and sertraline have been shown to be effective for this purpose. Paraphilias. The SSRIs may reduce obsessive-compulsive behavior in people with paraphilias. The SSRIs diminish the average time per day spent in unconventional sexual fantasies, urges, and activities. Evidence suggests a greater response for sexual obsessions than for paraphilic behavior. Autism. Obsessive-compulsive behavior, poor social relatedness, and aggression are prominent autistic features that may respond to serotonergic agents such as SSRIs and clomipramine (Anafranil). Sertraline and fluvoxamine have been shown in controlled and open-label trials to mitigate aggressiveness, self-injurious behavior, repetitive behaviors, some degree of language delay, and (rarely) lack of social relatedness in adults with autistic spectrum disorders. Fluoxetine has been reported to be effective for features of autism in children, adolescents, and adults. Precautions and Adverse Reactions SSRI side effects need to be considered in terms of their onset, duration, and severity. For example, nausea and jitteriness are early, generally mild, and time-limited side effects. Although SSRIs share common side effect profiles, individual drugs in this class may cause a higher rate or carry a more severe risk of certain side effects depending on the patient. Sexual Dysfunction All SSRIs cause sexual dysfunction, and it is the most common adverse effect of SSRIs associated with long-term treatment. It has an estimated incidence of between 50 and 80 percent. The most common complaints are anorgasmia, inhibited orgasm, and decreased libido. Some studies suggest that sexual dysfunction is dose related, but this has not been clearly established. Unlike most of the other adverse effects of SSRIs, sexual inhibition rarely resolves in the first few weeks of use but usually continues as long as the drug is taken. In some cases, there may be improvement over time. Strategies to counteract SSRI-induced sexual dysfunction are numerous, and none has been proven to be very effective. Some reports suggest decreasing the dosage or adding bupropion (Wellbutrin) or amphetamine. Reports have described successful treatment of SSRI-induced sexual dysfunction with agents such as sildenafil (Viagra), which are used to treat erectile dysfunction. Ultimately, patients may need to be switched to

antidepressants that do not interfere with sexual functioning, drugs such as mirtazapine or bupropion. Gastrointestinal Adverse Effects Gastrointestinal (GI) side effects are very common and are mediated largely through effects on the serotonin 5-HT3 receptor. The most frequent GI complaints are nausea, diarrhea, anorexia, vomiting, flatulence, and dyspepsia. Sertraline and fluvoxamine produce the most intense GI symptoms. Delayed-release paroxetine, compared with the immediate-release preparation of paroxetine, has less intense GI side effects during the first week of treatment. However, paroxetine, because of its anticholinergic activity, frequently causes constipation. Nausea and loose stools are usually dose related and transient, usually resolving within a few weeks. Sometimes flatulence and diarrhea persist, especially during sertraline treatment. Initial anorexia may also occur and is most common with fluoxetine. SSRI-induced

appetite and weight loss begin as soon as the drug is taken and peak at 20 weeks, after which weight often returns to baseline. Up to one third of persons taking SSRIs will gain weight, sometimes more than 20 lbs. This effect is mediated through a metabolic mechanism, increase in appetite, or both. It happens gradually and is usually resistant to diet and exercise regimens. Paroxetine is associated with more frequent, rapid, and pronounced weight gain than the other SSRIs, especially among young women. Cardiovascular Effects All SSRIs can lengthen the QT interval in otherwise healthy people and cause druginduced long QT syndrome, especially when taken in overdose. The risk of QTc prolongation increases when an antidepressant and an antipsychotic are used in combination, an increasingly common practice. Citalopram stands out as the SSRI with the most pronounced effect QT intervals. A QT study to assess the effects of 20-mg and 60-mg doses of citalopram on the QT interval in adults, compared with placebo, found a maximum mean prolongation in the individually corrected QT intervals were 8.5 milliseconds for 20 mg citalopram and 18.5 milliseconds for 60 mg. For 40 mg, prolongation of the corrected QT interval was estimated to be 12.6 milliseconds. Based on these findings, the FDA has issued the following recommendation regarding citalopram use: 20 mg a day is the maximum recommended dose for patients with hepatic impairment, who are older than 60 years of age, who are CYP2C19 poor metabolizers, or who are taking concomitant cimetidine (Tagamet). No longer prescribe at doses greater than 40 mg a day. Do not use in patients with congenital long QT syndrome. Correct hypokalemia and hypomagnesemia before administering citalopram. Monitor electrolytes as clinically indicated.

Consider more frequent electrocardiograms in patients with congestive heart failure, bradyarrhythmias, or patients on concomitant medications that prolong the QT interval. The fact that citalopram carries greater risk of causing fatal rhythm abnormalities was confirmed in a review of 469 SSRI poisoning admissions. Accordingly, patients should be advised to contact their prescriber immediately if they experience signs and symptoms of an abnormal heart rate or rhythm while taking citalopram. The effect of vilazodone (20, 40, 60, and 80 mg) on the QTc interval was evaluated and a small effect was observed. The upper bound of the 90 percent confidence interval for the largest placebo-adjusted, baseline-corrected QTc interval was below 10 milliseconds, based on the individual correction method (QTcI). This is below the threshold for clinical concern. However, it is unknown whether 80 mg is adequate to represent a high clinical exposure condition. Physicians should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in SSRI treated patients with prostate cancer as reductions in androgen levels can cause QTc interval prolongation. Dextromethorphan/Quinidine (Nuedexta) is available as a treatment for pseudobulbar affect, which is defined by involuntary, sudden, and frequent episodes of laughing or crying that are generally out of proportion or inappropriate to the situation. Quinidine that can prolong the QT interval is a potent inhibitor of CYP2D6. It should not be used with other medications that prolong the QT interval and are metabolized by CYP2D6. This drug should be used with caution with any medications that can prolong the QT interval and inhibit CYP3A4, particularly in patients with cardiac disease. Antepartum use of SSRIs is sometimes associated with QTc interval prolongation in exposed neonates. In a review of 52 newborns exposed to SSRIs in the immediate antepartum period and 52 matched control subjects, the mean QTc was significantly longer in the group of newborns exposed to antidepressants as compared with control subjects. Five (10 percent) newborns exposed to SSRIs had a markedly prolonged QTc interval (greater than 460 milliseconds) compared with none of the unexposed newborns. The longest QTc interval observed among exposed newborns was 543 milliseconds. All of the drug-

associated repolarization abnormalities normalized in subsequent electrocardiographic tracings. Headaches The incidence of headache in SSRI trials was 18 to 20 percent, only 1 percentage point higher than the placebo rate. Fluoxetine is the most likely to cause headache. On the other hand, all SSRIs are effective prophylaxis against both migraine and tension-type headaches in many persons. Central Nervous System Adverse Effects Anxiety. Fluoxetine may cause anxiety, particularly in the first few weeks of

treatment. However, these initial effects usually give way to an overall reduction in anxiety after a few weeks. Increased anxiety is caused considerably less frequently by paroxetine and escitalopram, which may be better choices if sedation is desired, as in mixed anxiety and depressive disorders. Insomnia and Sedation. The major effect SSRIs exert in the area of insomnia and sedation is improved sleep resulting from treatment of depression and anxiety. However, as many as 25 percent of persons taking SSRIs note trouble sleeping, excessive somnolence, or overwhelming fatigue. Fluoxetine is the most likely to cause insomnia, for which reason it is often taken in the morning. Sertraline and fluvoxamine are about equally likely to cause insomnia as somnolence, and citalopram and especially paroxetine often cause somnolence. Escitalopram is more likely to interfere with sleep than its isomer, citalopram. Some persons benefit from taking their SSRI dose before going to bed, but others prefer to take it the morning. SSRI-induced insomnia can be treated with benzodiazepines, trazodone (Desyrel) (clinicians must explain the risk of priapism), or other sedating medicines. Significant SSRI-induced somnolence often requires switching to use of another SSRI or bupropion. Other Sleep Effects. Many persons taking SSRIs report recalling extremely vivid dreams or nightmares. They describe sleep as “busy.” Other sleep effects of the SSRIs include bruxism, restless legs, nocturnal myoclonus, and sweating. Emotional Blunting. Emotional blunting is a largely overlooked but frequent side effect associated with chronic SSRI use. Patients report an inability to cry in response to emotional situations, a feeling of apathy or indifference, or a restriction in the intensity of emotional experiences. This side effect often leads to treatment discontinuation, even when the drugs provide relief from depression or anxiety. Yawning. Close clinical observation of patients taking SSRIs reveals an increase in yawning. This side effect is not a reflection of fatigue or poor nocturnal sleep but is the result of SSRI effects on the hypothalamus. Seizures. Seizures have been reported in 0.1 to 0.2 percent of all patients treated with SSRIs, an incidence comparable to that reported with other antidepressants and not significantly different from that with placebo. Seizures are more frequent at the highest doses of SSRIs (e.g., fluoxetine 100 mg a day or higher). Extrapyramidal Symptoms. The SSRIs may rarely cause akathisia, dystonia, tremor, cogwheel rigidity, torticollis, opisthotonos, gait disorders, and bradykinesia. Rare cases of tardive dyskinesia have been reported. Some people with well-controlled Parkinson’s disease may experience acute worsening of their motor symptoms when they take SSRIs.

Anticholinergic Effects Paroxetine has mild anticholinergic activity that causes dry mouth, constipation, and sedation in a dose-dependent fashion. Nevertheless, most persons taking paroxetine do not experience cholinergic adverse effects. Other SSRIs are associated with dry mouth, but this effect is not mediated by muscarinic activity. Hematologic Adverse Effects The SSRIs can cause functional impairment of platelet aggregation but not a reduction in platelet number. Easy bruising and excessive or prolonged bleeding manifest this pharmacological effect. When patients exhibit these signs, a test for bleeding time should be performed. Special monitoring is suggested when patients use SSRIs in conjunction with anticoagulants or aspirin. Concurrent use

of SSRIs and nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with a significantly increased risk of gastric bleeding. In cases where this combination is necessary, use of proton pump inhibitors should be considered. Electrolyte and Glucose Disturbances The SSRIs may acutely decrease glucose concentrations; therefore, diabetic patients should be carefully monitored. Long-term use may be associated with increased glucose levels, although it remains to be proven whether this is the result of a pharmacological effect. It is possible that antidepressant users have other characteristics that raise their odds of developing diabetes or are more likely to be diagnosed with diabetes or other medical conditions as a result of being in treatment for depression. Cases of SSRI-associated hyponatremia and the syndrome of inappropriate antidiuretic hormone have been seen in some patients, especially those who are older or treated with diuretics. Endocrine and Allergic Reactions The SSRIs can increase prolactin levels and cause mammoplasia and galactorrhea in both men and women. Breast changes are reversible upon discontinuation of the drug, but this may take several months to occur. Various types of rashes appear in about 4 percent of all patients; in a small subset of these patients, the allergic reaction may generalize and involve the pulmonary system, resulting rarely in fibrotic damage and dyspnea. SSRI treatment may have to be discontinued in patients with drug-related rashes. Serotonin Syndrome Concurrent administration of an SSRI with an MAOI, l-tryptophan, or lithium (Eskalith) can raise plasma serotonin concentrations to toxic levels, producing a constellation of symptoms called serotonin syndrome. This serious and possibly fatal syndrome of

serotonin overstimulation comprises, in order of appearance as the condition worsens, (1) diarrhea; (2) restlessness; (3) extreme agitation, hyperreflexia, and autonomic instability with possible rapid fluctuations in vital signs; (4) myoclonus, seizures, hyperthermia, uncontrollable shivering, and rigidity; and (5) delirium, coma, status epilepticus, cardiovascular collapse, and death. Treatment of serotonin syndrome consists of removing the offending agents and promptly instituting comprehensive supportive care with nitroglycerine, cyproheptadine (Periactin), methysergide (Sansert), cooling blankets, chlorpromazine (Thorazine), dantrolene (Dantrium), benzodiazepines, anticonvulsants, mechanical ventilation, and paralyzing agents. Sweating Some patients experience sweating while being treated with SSRIs. The sweating is unrelated to ambient temperature. Nocturnal sweating may drench bed sheets and require a change of night clothes. Terazosin (Hytrin), 1 or 2 mg per day, is often dramatically effective in counteracting sweating. Overdose The adverse reactions associated with overdose of vilazodone at doses of 200 to 280 mg as observed in clinical trials included serotonin syndrome, lethargy, restlessness, hallucinations, and disorientation. Selective Serotonin Reuptake Inhibitor Withdrawal The abrupt discontinuance of SSRI use, especially one with a shorter half-life such as paroxetine or fluvoxamine, has been associated with a withdrawal syndrome that may include dizziness, weakness, nausea, headache, rebound depression, anxiety, insomnia, poor concentration, upper respiratory symptoms, paresthesias, and migraine-like symptoms. It usually does not appear until after at least 6 weeks of treatment and usually resolves spontaneously in 3 weeks. Persons who experienced transient adverse effects in the first weeks of taking an SSRI are more likely to experience discontinuation symptoms. Fluoxetine is the SSRI least likely to be associated with this syndrome because the halflife of its metabolite is more than 1 week, and it effectively tapers itself. Fluoxetine has therefore been used in some cases to treat the discontinuation syndrome caused by termination of other SSRIs. Nevertheless, a delayed and attenuated withdrawal syndrome occurs with fluoxetine as well. DRUG INTERACTIONS The SSRIs do not interfere with most other drugs. A serotonin syndrome (Table 29.28-3) can develop with concurrent administration of MAOIs, l-tryptophan,

lithium, or other

antidepressants that inhibit reuptake of serotonin. Fluoxetine, sertraline, and paroxetine can raise plasma concentrations of TCAs, which can cause clinical toxicity. A number of potential pharmacokinetic interactions have been described based on in vitro analyses of the CYP enzymes, but clinically relevant interactions are rare. SSRIs that inhibit CYP2D6 may interfere with the analgesic effects of hydrocodone and oxycodone. These drugs can also reduce the effectiveness of tamoxifen (Nolvadex, Soltamox). Combined use of SSRIs and NSAIDs increases the risk of gastric bleeding. Table 29.28-3 Serotonin Syndrome Symptoms The SSRIs, particularly fluvoxamine, should not be used with clozapine because it raises clozapine concentrations, increasing the risk of seizure. The SSRIs may increase the duration and severity of zolpidem (Ambien)-induced side effects, including hallucinations. Fluoxetine Fluoxetine can be administered with tricyclic drugs, but the clinician should use low dosages of the tricyclic drug. Because it is metabolized by the hepatic enzyme CYP2D6, fluoxetine may interfere with the metabolism of other drugs in the 7 percent of the population who have an inefficient isoform of this enzyme, the so-called poor metabolizers. Fluoxetine may slow down the metabolism of carbamazepine (Tegretol), antineoplastic agents, diazepam (Valium), and phenytoin (Dilantin). Drug interactions have been described for fluoxetine that may affect the plasma levels of benzodiazepines, antipsychotics, and lithium. Fluoxetine and other SSRIs may interact with warfarin (Coumadin), increasing the risk of bleeding and bruising. Sertraline Sertraline may displace warfarin from plasma proteins and may increase the prothrombin time. The drug interaction data on sertraline support a generally similar profile to that of fluoxetine, although sertraline does not interact as strongly with the CYP2D6 enzyme. Paroxetine Paroxetine has a higher risk for drug interactions than does either fluoxetine or sertraline because it is a more potent inhibitor of the CYP2D6 enzyme. Cimetidine can increase the concentration of sertraline and paroxetine, and phenobarbital (Luminal) and phenytoin can decrease the concentration of paroxetine. Because of the potential

for interference with the CYP2D6 enzyme, the coadministration of paroxetine with other antidepressants, phenothiazines, and antiarrhythmic drugs should be undertaken with caution. Paroxetine may increase the anticoagulant effect of warfarin. Coadministration of paroxetine and tramadol may precipitate serotonin syndrome in elderly persons. Fluvoxamine Among the SSRIs, fluvoxamine appears to present the most risk for drug–drug interactions. Fluvoxamine is metabolized by the enzyme CYP3A4, which may be inhibited by ketoconazole (Nizoral). Fluvoxamine may increase the half-life of alprazolam, triazolam (Halcion), and diazepam, and it should not be coadministered with these agents. Fluvoxamine may increase theophylline levels threefold and warfarin levels twofold, with important clinical consequences; thus, the serum levels of the latter drugs should be closely monitored and the doses adjusted accordingly. Fluvoxamine raises concentrations and may increase the activity of clozapine, carbamazepine, methadone (Dolophine, Methadose), propranolol (Inderal), and diltiazem (Cardizem). Fluvoxamine has no significant interactions with lorazepam (Ativan) or digoxin (Lanoxin). Citalopram Citalopram is not a potent inhibitor of any CYP enzymes. Concurrent administration of cimetidine increases concentrations of citalopram by about 40 percent. Citalopram does not significantly affect the metabolism of, nor is its metabolism significantly affected by, digoxin, lithium, warfarin, carbamazepine, or imipramine (Tofranil). Citalopram increases the plasma concentrations of metoprolol (Lopressor) twofold, but this usually has no effect on blood pressure or heart rate. Data on coadministration of citalopram and potent inhibitors of CYP3A4 or CYP2D6 are not available.

Escitalopram Escitalopram is a moderate inhibitor of CYP2D6 and has been shown to significantly raise desipramine (Norpramin) and metoprolol concentrations. Vilazodone Vilazodone dose should be reduced to 20 mg when co-administered with CYP3A4 strong inhibitors. Concomitant use with inducers of CYP3A4 can result in inadequate drug concentrations and may diminish effectiveness. The effect of CYP3A4 inducers on systemic exposure of vilazodone has not been evaluated. LABORATORY INTERFERENCES The SSRIs do not interfere with any laboratory tests.

DOSAGE AND CLINICAL GUIDELINES Fluoxetine Fluoxetine is available in 10- and 20-mg capsules, in a scored 10-mg tablet, as a 90-mg enteric-coated capsule for once-weekly administration, and as an oral concentrate (20 mg/5 mL). Fluoxetine is also marketed as Sarafem for PMDD. For depression, the initial dosage is usually 10 or 20 mg orally each day, usually given in the morning, because insomnia is a potential adverse effect of the drug. Fluoxetine should be taken with food to minimize the possible nausea. The long half-lives of the drug and its metabolite contribute to a 4-week period to reach steady-state concentrations. Twenty milligrams is often as effective as higher doses for treating depression. The maximum dosage recommended by the manufacturer is 80 mg a day. To minimize the early side effects of anxiety and restlessness, some clinicians initiate fluoxetine use at 5 to 10 mg a day either with the scored 10-mg tablet or by using the liquid preparation. Alternatively, because of the long half-life of fluoxetine, its use can be initiated with an every-otherday administration schedule. The dosage of fluoxetine (and other SSRIs) that is effective in other indications may differ from the dosage generally used for depression. Sertraline Sertraline is available in scored 25-, 50-, and 100-mg tablets. For the initial treatment of depression, sertraline use should be initiated with a dosage of 50 mg once daily. To limit the GI effects, some clinicians begin at 25 mg a day and increase to 50 mg a day after 3 weeks. Patients who do not respond after 1 to 3 weeks may benefit from dosage increases of 50 mg every week up to a maximum of 200 mg given once daily. Sertraline can be administered in the morning or the evening. Administration after eating may reduce the GI adverse effects. Sertraline oral concentrate (1 mL = 20 mg) has 12 percent alcohol content and must be diluted before use. When used to treat panic disorder, sertraline should be initiated at 25 mg to reduce the risk of provoking a panic attack. Paroxetine Immediate-release paroxetine is available in scored 20-mg tablets; in unscored 10-, 30-, and 40-mg tablets; and as an orange-flavored 10-mg/5-mL oral suspension. Paroxetine use for the treatment of depression is usually initiated at a dosage of 10 or 20 mg a day. An increase in the dosage should be considered when an adequate response is not seen in 1 to 3 weeks. At that point, the clinician can initiate upward dose titration in 10-mg increments at weekly intervals to a maximum of 50 mg a day. Persons who experience GI upset may benefit by taking the drug with food. Paroxetine can be taken initially as a single daily dose in the evening; higher dosages may be divided into two doses per day. A delayed-release formulation of paroxetine, paroxetine CR, is available in 12.5-, 25-,

and 37.5-mg tablets. The starting dosages of paroxetine CR are 25 mg per day for depression and 12.5 mg per day for panic disorder. Paroxetine is the SSRI most likely to produce a discontinuation syndrome because plasma concentrations decrease rapidly in the absence of continuous dosing. To limit the development of symptoms of abrupt discontinuation, paroxetine use should be tapered gradually, with dosage reductions every 2 to 3 weeks. Fluvoxamine Fluvoxamine is the only SSRI not approved by the FDA as an antidepressant. It is indicated for social anxiety disorder and OCD. It is available in unscored 25-mg tablets and scored 50- and 100-mg tablets. The effective daily dosage range is 50 to 300 mg a day. A usual starting dosage is 50 mg once a day at bedtime for

the first week, after which the dosage can be adjusted according to the adverse effects and clinical response. Dosages above 100 mg a day may be divided into twice-daily dosing. A temporary dosage reduction or slower upward titration may be necessary if nausea develops over the first 2 weeks of therapy. Although fluvoxamine can also be administered as a single evening dose to minimize its adverse effects, its short half-life may lead to interdose withdrawal. An extended-release formulation is available in 100- and 150-mg dose strengths. All fluvoxamine formulations should be swallowed with food without chewing the tablet. Abrupt discontinuation of fluvoxamine may cause a discontinuation syndrome owing to its short half-life. Citalopram Citalopram is available in 20- and 40-mg scored tablets and as a liquid (10 mg/5 mL). The usual starting dosage is 20 mg a day for the first week, after which it usually is increased to 40 mg a day. For elderly persons or persons with hepatic impairment, 20 mg a day is recommended, with an increase to 40 mg a day only if there is no response at 20 mg a day. Tablets should be taken once daily in either the morning or the evening with or without food. Escitalopram Escitalopram is available as 10- and 20-mg scored tablets, as well as an oral solution at a concentration of 5 mg/5 mL. The recommended dosage of escitalopram is 10 mg per day. In clinical trials, no additional benefit was noted when 20 mg per day was used. Vilazodone Vilazodone is available as 10-, 20-, and 40-mg tablets. The recommended therapeutic dose of vilazodone is 40 mg once daily. Treatment should be titrated, starting with an initial dose of 10 mg once daily for 7 days, followed by 20 mg once daily for an additional 7 days, and then an increase to 40 mg once daily. Vilazodone should be taken with food. If vilazodone is taken without food, inadequate drug concentrations may

result and the drug’s effectiveness may be diminished. Vilazodone is not approved for use in children. The safety and efficacy of vilazodone in pediatric patients have not been studied. No dose adjustment is recommended on the basis of age. No dose adjustment is recommended in patients with mild or moderate hepatic impairment. Vilazodone has not been studied in patients with severe hepatic impairment. No dose adjustment is recommended in patients with mild, moderate, or severe renal impairment. Pregnancy and Breast-Feeding With the exception of paroxetine, the SSRIs are safe to take during pregnancy when deemed necessary for treatment of the mother. There are no controlled human data regarding vilazodone use during pregnancy nor are there human data regarding drug concentrations in breast milk. Transient QTc prolongation has been noted in newborns whose mother was being treated with an SSRI during pregnancy. Loss of Efficacy Some patients report a diminished response or total loss of response to SSRIs with recurrence of depressive symptoms while remaining on a full dose of medication. The exact mechanism of this so-called poop-out is unknown, but the phenomenon is very real. Potential remedies for the attenuation of response to SSRIs include increasing or decreasing the dosage, tapering drug use, and then rechallenging with the same medication, switching to another SSRI or non-SSRI antidepressant, and augmenting with bupropion or another augmentation agent. Vortioxetine (Brintellix) Vortioxetine works mainly as an inhibitor of serotonin (5-HT) reuptake, but it has a more complex pharmacologic profile than other SSRIS. It also acts as an agonist at 5HT1A receptors, a partial agonist at 5-HT1B receptors and an antagonist at 5-HT3, 5HT1D and 5-HT7 receptors. The contribution of each of these activities to the drug’s antidepressant effect has not been established, but it is the only compound with this combination of pharmacodynamic actions. Side effects seen during the trials include, but are not limited to, nausea, constipation and vomiting. The recommended starting dose is 10 mg administered orally once daily without regard to meals. The dose should then be increased to 20 mg/day, as tolerated. A dose of 5 mg/day should be considered for patients who do not tolerate higher doses. The maximum recommended dose of

Vortioxetine is 10 mg/day in known CYP2D6 poor metabolizers. Reduction of the dose of Vortioxetine by one half is suggested when patients are receiving a CYP2D6 strong inhibitor (e.g., bupropion, fluoxetine, paroxetine, or quinidine) concomitantly. The dose should be increased to the original dose of vortioxetine in patients who stop taking CYP inducers, (e.g., rifampin,

carbamazepine, or phenytoin) increasing its dose should be considered. This is especially important when a strong CYP inducer is coadministered for greater than 14 days. The maximum recommended dose should not exceed three times the original dose. The dose of vortioxetine should be reduced to the original level within 14 days, when the inducer is discontinued. Although vortioxetine can be abruptly discontinued, in placebo-controlled trials patients experienced transient adverse reactions such as headache and muscle tension following abrupt discontinuation of vortioxetine 15 mg/day or 20 mg/day. To avoid these adverse reactions, it is recommended that the dose be decreased to 10 mg/day for one week before full discontinuation of vortioxetine 15 mg/day or 20 mg/day Vortioxetine is available in 5 milligram (mg), 10 mg, 15 mg and 20 mg tablets. REFERENCES Ashton AK, Longdon MC. SSNRI-induced, dose dependent, nonmenstrual, vaginal spotting and galactorrhea accompanied by prolactin elevation (Letter). Am J Psychiatry. 2007;164:1121. Baldessarini RJ, Pompili M, Tondo L. Suicidal risk in antidepressant drug trials. Arch Gen Psychiatry. 2006;63:246. Barbui C, Esposito E, Cipriani A. Selective serotonin reuptake inhibitors and risk of suicide: A systematic review of observational studies. CMAJ. 2009;180:291. Chambers CD, Hernandez-Diaz S, Van Marter LJ, Werler MM, Louik C. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. N Engl J Med. 2006;354:579. Cipriani A, Barbui C, Brambilla P, Furukawa TA, Hotopf M. Are all antidepressants really the same? The case of fluoxetine: A systematic review. J Clin Psychiatry. 2006;67:850. Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JPT. Comparative efficacy and acceptability of 12 new-generation antidepressants: A multiple-treatments meta-analysis. Lancet. 2009;373:746. Clayton A, Kornstein S, Prakash A, Mallinckrodt C, Wohlreich M. Changes in sexual functioning associated with duloxetine, escitalopram, and placebo in the treatment of patients with major depressive disorder. J Sex Med. 2007;4:917. Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA. 2006;295:499. Couturier J, Sy A, Johnson N, Findlay S. Bone mineral density in adolescents with eating disorders exposed to selective serotonin reuptake inhibitors. Eat Disord. 2013;21(3):238. Cowen P, Sherwood AC. The role of serotonin in cognitive function: Evidence from recent studies and implications for understanding depression. J Psychopharmacol. 2013;27(7):575. Diem SJ, Blackwell TL, Stone KL, Yaffe K, Haney EM. Use of antidepressants and rates of hip bone loss in older women: The study of osteoporotic fractures. Arch Intern Med. 2007;167:1240. Glassman AH, O'Connor CM, Califf RM, Swedberg K, Schwartz P. Association of low bone mineral density with selective serotonin reuptake inhibitor use by older men. Arch Intern Med. 2007;167(12):1246. Hu X-Z, Rush AJ, Charney D, Wilson AF, Sorant AJM. Association between a functional serotonin transporter promoter polymorphism and citalopram treatment in adult outpatients with major depression. Arch Gen Psychiatry. 2007;64:783. Looper KL. Potential medical and surgical complications of serotonergic antidepressant medications. Psychosomatics. 2007;48:1. Nurnberg GH, Hensley PL, Heiman JR, Croft HA, Debattista C. Sildenafil treatment of women with antidepressantassociated sexual dysfunction: A randomized controlled trial. JAMA. 2008;300:395. Sussman N. Selective serotonin reuptake inhibitors. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock's

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