Nonantimicrobial Effects of Antibacterial Agents

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One of the major advances in modern medicine was the development of antimicrobial chemotherapy. However, many antibacterial agents have unexpected or undesirable nonantimicrobial effects on humans. Microbes and man share many essentials of life, including DNA, adenosine triphosphate, and other biochemical pathways. Hence, some of these nonantimicrobial effects may also turn out to be pharmacologically useful. Oral hypoglycemic agents (i.e., sulfonylureas) and a certain diuretic agent (acetazolamide) are derivatives of sulfonamides. Erythromycin has been used clinically for its stimulatory effect on gastrointestinal motility. Macrolides, lincosamides, and tetracyclines have been known for their immunomodulatory effects. A tetracycline has been used to treat the syndrome of inappropriate antidiuretic hormone. Aminoglycosides may influence mucus production in patients with cystic fibrosis. Other antimicrobials may have side effects that are not therapeutically useful, such as osmotic diuresis with high-dose β-lactam administration, neuromuscular blockade of aminoglycosides, dysglycemia of fluoroquinolones, and serotonin syndrome with oxazolidinones.

The discovery of antimicrobial agents is one of the greatest advances in modern medicine. Antimicrobial agents interact with targets on bacteria, thus suppressing their growth and eventually destroying them. An ideal antimicrobial agent targets the microbes without affecting mammalian cells. However, because microbes and man share many essentials of life, including DNA, adenosine triphosphate (ATP), and other biochemical pathways, it is inevitable that antimicrobial agents will have nonantimicrobial effects that may be unexpected or undesirable. Occasionally, these "undesired effects" can be therapeutically useful. Minor changes in structure can alter the pharmacologic properties of a compound. Pharmacologically useful agents with nonantimicrobial therapeutic activities have been derived from known side effects of antimicrobial agents (table 1). The present article attempts to review the nonantimicrobial effects of commonly prescribed antibacterial agents, with emphasis on the common clinical applications of 'these agents.

SULFONAMIDES

Modern chemotherapy began in 1932, when Domagk reported protective effects of prontosil against murine streptococcal infections [1]. This development led to the discovery of numerous compounds with enhanced activity against microbes. Sulfonamides have a base structure that is similar to that of *p*-aminobenzoic acid, a factor necessary for the synthesis of folic acid by bacteria [2]. Some of the unwanted effects of sulfonamides have led to the development of sulfonamide-related agents that lack antimicrobial activity. These agents became more commonly used than their antimicrobial-active parent molecule.

Hypoglycemia. In 1942, Janbon and colleagues noted that some sulfonamides produced a hypoglycemic effect in animals [1]. Carbutamide became the first sulfonyurea to be used clinically for the treatment of diabetes [2]. Later, tolbutamide was the first sulfonylurea to be widely used clinically. Sulfonylureas exert their hypoglycemic effect by stimulating the release of insulin from pancreatic β cells and by increasing the sensitivity of peripheral tissues to insulin. Numerous other sulfonylureas have been developed since 1942 and are used clinically today for the treatment of diabetes.

Carbonic anhydrase inhibition. When sulfanilamide was introduced, metabolic acidosis was recognized as a side effect [1, 2]. Sulfanilamide was found to inhibit the carbonic anhydrase enzyme, which dehydrates bicarbonate to carbon dioxide. Blockade of carbonic anhydrase results in the excretion of bicarbonate and sodium, thereby causing diuresis. A number of sulfonamides were synthesized and tested for their ability to inhibit carbonic anhydrase. Acetazolamide was the most extensively studied derivative; however, its usefulness as a diuretic agent is limited to the treatment of open-angle glaucoma. Car-

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Table 1. Mechanism of antibacterial action and nonantimicrobial effects of commonly prescribed antimicrobial agents.

Antimicrobial class	Proposed mechanism of action	Nonantimicrobial effect(s)
Sulfonamides	Interference with the synthesis of folic acid through competitive inhibition of dihydropteroate synthase	Glycemic: Sulfonamides were found to produce hypoglycemia in animals. Sulfonylureas were derived from sulfonamides. Carbonic anhydrase inhibition: Sulfanilamide was found to inhibit carbonic anhydrase. Acetazolamide was later derived and is used clinically today for open-angle glaucoma.
Macrolides	Inhibition of bacterial protein synthesis through reversible binding to the 50S ribosomal subunit	Gastrointestinal motility: Erythromycin is used clinically for its promotility effects. Immunomodulation: Studies have evaluated macrolides for use in hypersecretory conditions and chronic airway inflammation disorders. Effect on respiratory secretion: Clarithromycin has been shown to decrease secretion production.
Lincosamides	Inhibition of bacterial protein synthesis through reversible binding to the 50S ribosomal subunit	Immunomodulation: Clindamycin is commonly used in addition to penicillins for the treatment of serious infections due to group A *Streptococcus pyogenes,* because it inhibits toxin production and enhances phagocytic activity.
Tetracyclines	Inhibition of bacterial protein synthesis through reversible binding to the 30S ribosomal subunit	Immunomodulation: Tetracyclines have been evaluated for their use in periodontal disorders, inflammatory disorders, and cancer therapy. Neuroprotection: There has been increased interest in the use of minocycline as a neuroprotective agent for the treatment of such conditions as spinal cord injuries, multiple sclerosis, or focal ischemic brain injury. SIADH: Demeclocycline has clinically been used for the treatment of SIADH.
Aminoglycosides	Inhibition of bacterial protein synthesis through irreversible binding to the 30S ribosomal subunit interfering with the reading of the genetic code	Neuromuscular blockade: An effect that has been associated with various aminoglycosides. *CFTR* gene: Gentamicin has been shown to restore *CFTR* function in patients with cystic fibrosis. Additional research is needed.
Fluoroquinolones	Inhibition of bacterial DNA topoisomerases required for bacterial DNA replication, transcription, repair, and recombination	Dysglycemia: Fluoroquinolones have been reported to have an effect on glucose homeostasis that is presently suspected to be the result of stimulation of pancreatic cells. Additional research is warranted to define the mechanism of the effect of fluoroquinolones on glucose homeostasis and to ascertain whether it is a class effect.
Oxazolidinones	Inhibition of bacterial protein synthesis by selectively binding to the 23S rRNA of the 50S ribosomal subunit	Serotonin syndrome: Linezolid is a reversible, nonselective inhibitor of monoamine oxidase, and several case reports of serotonin syndrome have been reported.
β-Lactams	Interfere with cell wall synthesis through binding to penicillin-binding proteins that are associated with the bacterial cell membrane	Platelet inhibition: All penicillins have been found to inhibit platelet aggregation in vitro to varying degrees. Disulfiram-like reactions: Certain cephem antibiotics, such as cefoperazone sodium, cefamandole, cefmetazole, and cefotetan, have an MTT side chain and are known to cause increased blood aldehyde concentrations. Osmotic diuresis: When given in high doses, carbenicillin and ticarcillin behave as a nonreabsorbable anion.

NOTE. *CFTR,* cystic fibrosis transmembrane regulator; MTT, methyl-tetrazol-thiol; SIADH, the syndrome of inappropriate antidiuretic hormone.

bonic anhydrase is present in nonrenal tissues, including the eye [2]. Carbonic anhydrase mediates the formation of large amounts of bicarbonate in the aqueous humor in the ciliary processes of the eye [2]. Inhibition of carbonic anhydrase decreases the rate of formation of aqueous humor and, consequently, reduces intraocular pressure.

MACROLIDES

The term "macrolide" is derived from the structure of a macrocyclic lactone nucleus to which different sugars are attached. The size of the lactone ring and the changes in the attachments either to the ring or to the type and position of the sugar residues give rise to the differences in antimicrobial activity and in the severity of gastrointestinal side effects [3]. The first macrolide, erythromycin, a 14-member ring molecule, was discovered >50 years ago. Erythromycin is still used clinically today, although its gastrointestinal side effects and the introduction of newer macrolides have limited its use as an antibacterial agent. Two nonantibacterial effects of macrolides—gastrointestinal motility and immunomodulation—are reviewed below.

Gastrointestinal motility. When given in therapeutic and subtherapeutic antimicrobial doses, erythromycin has a stimulatory effect on gastrointestinal motility, because it disrupts the motor patterns of the intestine in animals and humans before and after consumption of a meal [4]. Clinical studies have suggested that erythromycin and other 14-member ring macrolides act as a motilin receptor agonist [5, 6]. Motilin, an amino acid peptide, is believed to play a role in controlling the

cyclic bursts of contractile activity that occur in the gastrointestinal tract during the fasting state [7, 8]. Studies have suggested that a possible structure-activity relationship exists that would explain the affinity of the macrolide for the motilin receptor. Unlike erythromycin, macrolides with a 16-member ring (e.g., josamycin) were not found to stimulate gastrointestinal motility [5, 9, 10]. Of a group of volunteer subjects who were given erythromycin, 21% experienced abdominal cramps, nausea, vomiting, or diarrhea, compared with none of the patients who were treated with josamycin [3].

Derivatives of erythromycin that enhance gastrointestinal motility but lack antimicrobial properties are under development. These derivatives, if developed, would ease the concern regarding the use of low-dose erythromycin and its effect on antimicrobial resistance [11]. At present, for the treatment of conditions associated with gastrointestinal hypomotility, erythromycin offers the clinician an alternative therapeutic agent based on a different mechanism of action than that of the presently available agents.

Immunomodulation. Erythromycin and other macrolides have beneficial immunomodulatory effects [12–16]. Macrolide antibiotics have been found to be beneficial in the treatment of hypersecretory conditions, such as diffuse panbronchiolitis (DPB) and cystic fibrosis (CF) [12]. DPB is universally considered to be fatal unless it is treated with low-dose, long-term erythromycin therapy. *Pseudomonas aeruginosa* is a common organism isolated from infected patients. Macrolides have dramatically decreased morbidity and mortality and have also improved pulmonary function among patients with DPB [17]. Recently, Saiman et al. [13] evaluated the use of azithromycin as therapy for patients with CF who had chronic infection due to *P. aeruginosa*. When patients were randomized to receive either azithromycin or placebo, those who received azithromycin were found to have improvements in pulmonary function, nutritional function, and quality of life, as well as lower rates of pulmonary exacerbation. Because the macrolide class of antibacterial antibiotics does not have significant antipseudomonal activity, the improvement cannot be attributed to an antibacterial effect. The mechanism by which macrolides are effective in the treatment of hypersecretory conditions, such as DPB and CF, is not completely understood.

Several theories have been proposed regarding the effectiveness of macrolides in the treatment of hypersecretory conditions. First, macrolides have immunomodulating effects on different pathways of the inflammatory process; therefore, they reduce migration of neutrophils to the site by suppressing neutrophil chemotactic activity in the lungs [14, 18, 19]. Macrolides may also directly or indirectly alter neutrophil functions, because they achieve high intracellular concentrations [14–16, 20, 21]. Second, macrolides have a direct effect on the CF transmembrane regulator *(CFTR)* gene [22]. Third, the immunomodulatory effect of macrolides is based on their antioxidant action [16, 18, 20]. Treatment with erythromycin significantly decreased the intracellular oxidative burst capacity in neutrophils [20]. Other studies have suggested that macrolides have a beneficial effect on the release of cytokines, including prostaglandin E_2 and TNF-α, and on production of nitric oxide [16]. Saiman et al. [13] evaluated azithromycin for its effect on 2 inflammatory markers—IL-8 and neutrophil elastase—in patients with CF, and they found that patients who were given azithromycin had a significant decrease in neutrophil elastase but no change in the production of IL-8.

The immunomodulatory properties of macrolides may be therapeutically beneficial to patients with chronic airway inflammation, including chronic sinusitis, chronic obstructive pulmonary disease, and asthma [23]. Macrolides have been shown to have a steroid-sparing effect in patients with asthma and to have mucoregulatory properties [23]. Clarithromycin was evaluated for its effect on sputum production in patients with chronic respiratory tract infections [24]. Clarithromycin significantly decreased sputum production without altering either the total number of bacterial colony–forming units per gram of sputum or the bacterial flora in the sputum samples.

As biological response modifiers, macrolides may be of benefit in the treatment of chronic respiratory illnesses. Large-scale, randomized, placebo-controlled trials are needed to confirm the effectiveness of macrolides for the treatment of these conditions and to determine the long-term consequence of prolonged use of macrolide antibiotics. This information may lead to the development of related compounds that enhance immunomodulatory properties but lack antimicrobial properties.

LINCOSAMIDES

Clindamycin, a lincosamide antibiotic, is chemically unrelated to macrolides, but it possesses many biologic properties that are similar to those of macrolides, including its effect on the 50S ribosome. Clindamycin is commonly used in combination with a penicillin for the treatment of serious group A *Streptococcus pyogenes* infections. There are 3 potential reasons for the addition of clindamycin to the treatment for these cases, including (1) clindamycin's ability to suppress bacterial toxin synthesis; (2) its immunomodulatory effects; and (3) the absence of an inoculum effect, because clindamycin acts on the ribosome [25–29].

S. pyogenes organisms bear an M protein, a molecule that enhances bacterial virulence, on their surfaces [30, 31]. Strains that are rich in M proteins are known to impede opsonization by normal human serum and subsequent phagocytosis by human polymorphonuclear leukocytes [32]. Gemmell et al. [25] evaluated an M protein–positive strain of *S. pyogenes* grown in various concentrations of clindamycin at levels below the MIC. The streptococci that were exposed to clindamycin during the

growth phase were found to have inhibition of M protein synthesis. The authors suggested that certain antibiotics, such as clindamycin, might enhance the uptake of microorganisms by the phagocytic cells of the host. These immunomodulatory effects of clindamycin may be one reason for the greater efficacy of clindamycin in the treatment of infections due to *S. pyogenes,* compared with the efficacy of penicillins used alone.

TETRACYCLINES AND THEIR DERIVATIVES

Tetracyclines have been therapeutically useful agents for decades because of their broad antimicrobial activity. In addition, tetracyclines have been shown to have broad activity against an array of mediators of the inflammatory cascade. The beneficial effects of tetracyclines on immunomodulation and the effects of tetracyclines on the secretion of antidiuretic hormone are reviewed below.

Immunomodulation. Tetracyclines have been frequently used for the treatment of periodontal disorders, because of their antimicrobial properties. In 1983, Golub et al. [33] discovered an important nonantimicrobial property that would further support the use of tetracyclines for periodontal and other disorders. Tetracyclines have the ability to inhibit matrix metalloproteinases (MMPs), probably because of their ability to chelate zinc from the active site of MMPs [34–39]. MMPs belong to a family of enzymes that require 2 Zn^{++} ions per molecule to be active [37]. MMPs can play a vital role in the breakdown of the extracellular matrix physiologic function, including wound healing, bone resorption, and mammary involution [37]. In addition, MMPs can contribute to pathological conditions, including rheumatoid arthritis, coronary artery disease, and cancer, and they have been associated with the invasiveness and metastatic potential of tumor cells and are believed to promote the growth of the metastasized tumor. Tetracyclines have been studied for their potential use in cancer therapy, on the basis of their anti-MMP activity [38–41]. Additional research is needed to determine the effectiveness of tetracyclines and to ascertain whether they have a clinical role in cancer therapy.

Tetracyclines have also been reported to directly or indirectly decrease a variety of other inflammatory mediators, such as TNF, IL-1, neutrophil elastase, nitric oxide, and reactive oxygen intermediates [35, 42–53]. All of these inflammatory mediators are known to have a role in acute and chronic inflammatory disorders.

Tetracyclines may also play a vital role in the future of the treatment of superantigen-induced toxic shock, on the basis of their ability to down-regulate various proinflammatory cytokines and chemokines induced by staphylococcal exotoxin [43]. Shapira et al. [43] suggested that doxycycline may alter the pathophysiology of toxic shock and that it may have potential usefulness in the treatment of superantigen-induced toxic shock. Doxycycline was reported to block lipopolysaccharide-induced IL-1 in epithelial cells and to prevent lethal endotoxemia in vivo [42]. Thus, tetracyclines have a unique advantage in modifying a variety of inflammatory mediators, which makes them attractive agents for the treatment of acute and chronic inflammatory disorders, including gingivitis, rheumatoid arthritis, osteoarthritis, and acute respiratory distress syndrome.

The downside to the usefulness of the tetracyclines that are currently available for the treatment of inflammatory disorders is the concern about the emergence of antibiotic resistance as a result of the antimicrobial activity of tetracyclines. To overcome this concern, nonantimicrobial, chemically modified tetracyclines have been synthesized that lack antimicrobial activity while retaining their potent inhibition of inflammatory mediators [48, 54].

Therefore, tetracyclines are excellent candidates for investigation as drugs for the treatment of inflammatory disorders, including osteoarthritis. The National Institutes of Health trial is the first large trial to evaluate a tetracycline for the treatment of an inflammatory disorder [55].

Neuroprotection. Recently, there has been increased interest in the use of minocycline, a second-generation tetracycline, as a neuroprotective agent. The neuroprotective effect of minocycline is believed to be the result of its inhibition of mitochondrial release of cytochrome *c* and reactive microgliosis [56]. As a result of this discovery, minocycline has been evaluated in animal studies involving many different brain diseases [57–59]. Additional research will determine whether minocycline may be useful as a neuroprotective agent for the treatment of such conditions as acute spinal cord injury, multiple sclerosis, or focal ischemic brain injury.

The syndrome of inappropriate antidiuretic hormone (SIADH). Demeclocycline is a tetracycline antibiotic that has antibacterial activity similar to that of other tetracyclines. The main clinical use of demeclocycline is in the treatment of SIADH. SIADH is a disorder of normal osmoregulation of body fluids that results in the retention of free water and, hence, in hypervolemia. Singer and Rotenberg [60] observed demeclocycline-induced polyuria in a group of patients treated for skin disorders. These investigators concluded that demeclocycline had the ability to inhibit both the formation and the action of cyclic adenosine monophosphate in the collecting duct of the renal tubule. Demeclocycline appears to produce a predictable, reversible, and dose-dependent nephrogenic diabetes inspidus when given in doses of 600–1200 mg/day [60]. Several reports have documented the effectiveness of demeclocycline in the treatment of SIADH [61, 62]. Hence, demeclocycline has been recommended for patients with SIADH who do not readily respond to fluid restriction.

AMINOGLYCOSIDES

Aminoglycosides have been used for decades because of their activity against an array of gram-negative pathogens. We will review the neuromuscular blockade properties of aminoglycosides and, in addition, the use of aminoglycosides in the treatment of patients with CF.

Neuromuscular blockade. In 1956, Pridgen [63] reported a case of respiratory depression resulting from neomycin-ether interaction. Neuromuscular blockade has been observed in association with the use of various aminoglycosides, including neomycin, streptomycin, kanamycin, tobramycin, gentamicin, amikacin, and netilmicin [64–75]. Neuromuscular blockade is a rare but serious and potentially lethal adverse effect that is secondary to aminoglycoside administration and that is responsible for respiratory failure and delay in the weaning of a patient from a ventilator. The risk of aminoglycoside-induced neuromuscular blockade appears to increase in association with the presence of certain clinical conditions (e.g., underlying renal disease, underlying neuromuscular disease, botulism, and hypocalcemia) or with the concomitant administration of muscular relaxants (e.g., d-tubocurarine, succinylcholine chloride, or similar anesthetic agents) [64, 65, 75–79].

Animal studies that have evaluated neuromuscular blockade have indicated that aminoglycosides inhibit the presynaptic release of acetylcholine and prevent the internalization of calcium into the presynaptic region of the axon [66, 67, 77, 80, 81]. The calcium internalization must occur before the release of acetylcholine. Furthermore, animal studies have shown that aminoglycosides can blunt the response of postsynaptic receptors to acetylcholine [80, 82]. These studies have helped to delineate the differences in the neuromuscular blockade produced by the aminoglycosides, because they share a common chemical structure but can produce a neuromuscular blockade differently [75]. Neomycin is more active at the presynaptic junction, whereas streptomycin or netilmicin is more active at the postsynaptic junction [66, 75, 80, 82].

Calcium gluconate has been found to be effective in reversing aminoglycoside-induced neuromuscular blockade and is the preferred treatment [83]. Neostigmine has also been found to be effective; however, the associated response is variable [75].

CFTR *gene.* CF, a lethal, autosomal recessive genetically inherited disease, most commonly affects white populations [84–86]. The disease is caused by a mutation in the *CFTR* gene that leads to dysfunction of the CFTR protein [87]. Premature stop mutations within the gene are relatively common among patients with CF [87]. The CFTR protein regulates the transport of chloride and sodium in secretory epithelial cells, and a dysfunction in the CFTR protein leads to production of viscous secretions [87]. Patients with CF commonly have respiratory infections due to *Staphylococcus aureus* and *P. aeruginosa.* Because of their antimicrobial activity, aminoglycosides have frequently been used for the treatment of CF, primarily against infections due to *P. aeruginosa.*

In addition to their antimicrobial activity, aminoglycosides may have an additional benefit for certain patients with CF, in that they suppress premature termination codons, which allow for translation to continue to the normal end of the transcript [88–90]. Recently, Wilschanski et al. [91] evaluated the effects of topical gentamicin on *CFTR* function in the nasal mucosal cells of patients with CF. Patients received 2 drops of gentamicin or placebo in each nostril 3 times daily for 14 days. Gentamicin restored the *CFTR* function in ~90% of patients with CF who had stop mutations in the *CFTR* gene. Gentamicin appeared to be more effective in patients who are homozygous for stop mutations than in patients who are heterozygous for stop mutations. The mechanism for suppression of the premature termination codons by aminoglycosides is thought to be the binding to the decoding center of rRNA during translation of nonsense transcripts [91]. An alteration of the RNA conformation is a result of this binding, which reduces the accuracy of the codon-anticodon pairing [91]. Additional research is needed to determine the clinical application of aminoglycosides for regulation of the *CFTR* gene.

FLUOROQUINOLONES

Since the introduction of fluoroquinolones (FQs) in the 1980s, FQs have been extensively used to treat a variety of infections. FQs are among the most frequently prescribed agents because of their broad spectrum of activity, good tolerability, and excellent oral absorption. However, this class of agents is not exempt from having nonantimicrobial effects.

Fluoroquinolones have been reported to have an effect on glucose homeostasis [92–95]. Menzies et al. [93] presented reports of 3 patients who had gatifloxacin-induced hypoglycemia. All 3 patients were elderly and had a history of type 2 diabetes mellitus while receiving oral hypoglycemic agents. For each patient, the serum glucose level decreased significantly after the administration of gatifloxacin and returned to a level considered to be normal after discontinuation of gatifloxacin.

The exact mechanism of the effect of FQs on glucose homeostasis is unknown. There have been no reports of a pharmacokinetic interaction between gatifloxacin and oral hypoglycemic agents. A study of patients with non–insulin-dependent diabetes mellitus (NIDDM) who were receiving maintenance therapy with glyburide found no effect of gatifloxacin on glucose homeostasis [96]. On the other hand, Gajjar et al. [94] evaluated the effects of gatifloxacin on the glucose levels of patients with NIDDM whose conditions were maintained only through diet and exercise. Gatifloxacin was found to have no effect on glucose homeostasis, pancreatic

β cell function, or long-term serum glucose levels during fasting. However, gatifloxacin did produce a modest, transient increase in the serum levels of insulin at 1 h after administration of the dose given on day 1. Gajjar et al. [94] suggested that there may possibly be a direct stimulatory effect of gatifloxacin on pancreatic β cell function. Maeda et al. [97] found that, in rats, various FQs can increase the release of insulin from pancreatic islet cells. Recently, Zunkler and Wos [98] reported the effects of 2 FQs on the K^+/ATP pump in the β cells of the pancreas. Lomefloxacin increased insulin secretion, whereas norfloxacin produced minimal effects. Thus, it is postulated that different FQs may have variable effects on the K^+/ATP pump in the β cells of the pancreas. Additional research is needed to elucidate the exact mechanism of the effect of FQs on glucose homeostasis and to ascertain whether this is a class effect.

OXAZOLIDINONES

Linezolid is the first agent of a new class of antibacterial antibiotics, the oxazolidinones, recently approved by the US Food and Drug Administration (Rockville, MD) for the treatment of resistant gram-positive infections, including infections due to vancomycin-resistant enterococci and methicillin-resistant staphylococci.

Linezolid is a reversible, nonselective inhibitor of monoamine oxidase [99]. Therefore, a potential exists for interaction with adrenergic and serotonergic agents. In study volunteers, linezolid can potentiate adrenergic effects of phenylpropanolamine or pseudoephedrine [100]. Coadministration of linezolid and serotonergic agents was not associated with serotonin syndrome in phase 1, 2, or 3 clinical studies [99, 101]. Since the approval of linezolid by the US Food and Drug Administration, several cases of serotonin syndrome have been reported in association with the concurrent use of linezolid and selective serotonin reuptake inhibitors (i.e., paroxetine hydrochloride, citalopram, and sertraline) [102–105]. Serotonin syndrome is a potentially serious adverse event. Serotonin syndrome typically presents as neuromuscular hyperactivity (i.e., tremors, clonus, myclonus, and hyperreflexia), altered mental status, and autonomic hyperactivity (i.e., diaphoresis, fever, mydriasis, tachycardia, and tachypnea) [106]. The management of serotonin syndrome is largely supportive.

β-LACTAMS

β-Lactam antibiotics have 3 known nonantibacterial activities, including platelet inhibition, disulfiram-like reaction (associated with the presence of the methyl-tetrazol-thiol side chain), and osmotic diuresis. These activities have no therapeutic use and will not be discussed further in the present article.

CONCLUSION

Antimicrobial chemotherapy has resulted in the cure of potentially life-threatening infections and, also, in the realization that drugs may have unexpected or undesired effects other than their intended effects. Erythromycin has been used clinically for its stimulatory effect on gastrointestinal motility. Additional research will determine whether therapeutic agents will be derived from either macrolides or tetracyclines for their immunomodulatory properties. Knowledge of these unintended effects may be helpful, because therapeutic agents or therapeutic indications have been derived from these antibacterial agents.

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Note added in proof. Since this article was accepted for publication, a study has been published that has reported that moxifloxacin, gatifloxacin, and levofloxacin were shown to have inhibitory effects on leukocyte transendothelial migration and chemokine production by endothelial cells in response to infection or proinflammatory cytokines (Uriarte SM, Molestina RE, Miller RD, et al. Effects of fluoroquinolones on the migration of human phagocytes through *Chlamydia pneumoniae*–infected and tumor necrosis factor alpha–stimulated endothelial cells. Antimicrob Agents Chemother **2004**; 48:2538–43).