Trospium Chloride: A Quaternary Amine with Unique Pharmacologic Properties

Raymond W. Pak, MD, Steven P. Petrou, MD, and David R. Staskin, MD*

Address
*Department of Urology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA.
E-mail: petrou.steven@mayo.edu

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The mainstay of pharmacologic treatment of overactive bladder is anticholinergic therapy. Cholinergic blockade is efficacious in decreasing the symptoms of urgency, frequency, and urge incontinence, but also is associated with undesirable side effects such as dry mouth, blurred vision, constipation, and central nervous system side effects. The property of anticholinergic agents that has been associated with increased efficacy and tolerability is receptor specificity. The safety of anticholinergic agents has been associated with the pharmacokinetics, metabolism, protein binding, and ability to penetrate the blood brain barrier. Trospium chloride, available in Europe for more than 20 years and under review by the US Food and Drug Administration for the treatment of overactive bladder, is a quaternary amine that is minimally metabolized, not highly protein-bound, and theoretically should not cross the blood brain barrier. Some of the characteristics of this unique anticholinergic agent are reviewed in this article and the relative contributions of these factors are discussed.

Introduction

Pharmacologic intervention for overactive bladder is anticholinergic therapy. The presumed primary mode of action is to alter the bladder efferent neural pathways at the postganglionic parasympathetic receptor sites [1,2••,3]. Immediate-release oxybutynin, extended release oxybutynin, oxybutynin transdermal delivery system, immediate-release tolterodine, and tolterodine LA make up more than 98% of the marketplace. In 2004, it is anticipated that three new anticholinergic agents will be released in the United States for the treatment of overactive (OAB). These new agents are darifenacin, solifenacin, and trospium chloride.

Of the three new agents, trospium chloride has been used extensively in Europe for more than 20 years. Its clinical efficacy and safety have been demonstrated during that time, although the pharmacology and mode of action, as with all of the agents mentioned previously, is not understood completely. A unique combination of properties of trospium chloride may potentially contribute to an improved therapeutic index. Trospium chloride is relatively unique because it is a quaternary amine, has a high-affinity equipotent binding to all of the muscarinic subtypes, undergoes minimal metabolism, and demonstrates low serum protein-binding and very low lipophilicity, which are characteristics that contribute to its safety and efficacy profile.

In this article, the attributes of trospium chloride are reviewed and are compared with properties of other existing drugs and drugs that are in development for OAB.

Chemical Structure: Tertiary Versus Quaternary Amines

The anticholinergic agents used for treating OAB are amines, derivatives of ammonia in which one or more of the hydrogen atoms are replaced by alkyl or aryl groups. Amines are classified as primary, secondary, tertiary, or quaternary based on the number of substitutions. As a class, quaternary amines have hydrophilic properties with a low oil-to-water partition coefficient, which make it difficult for them to cross lipid cell membranes. Quaternary amines are poorly absorbed from the gastrointestinal tract, have low bioavailability, and have poor central nervous system (CNS) penetration. They are commonly referred to as peripherally acting because of their inability to traverse the CNS blood brain barrier.

Oxybutynin, tolterodine, darifenacin, and solifenacin are tertiary amines; trospium chloride and propantheline are quaternary amines [4••,5]. The chemical structures of oxybutynin, tolterodine, and trospium chloride are depicted in Figure 1 [6,7]. The major difference between tertiary and quaternary amines is the (+) charge and hydrophilic nature of trospium chloride, a quaternary amine. This is in contrast to tertiary amines, which, as a class, are not charged and are lipophilic in nature. These compounds tend to have greater oral bioavailability than quaternary amines and more

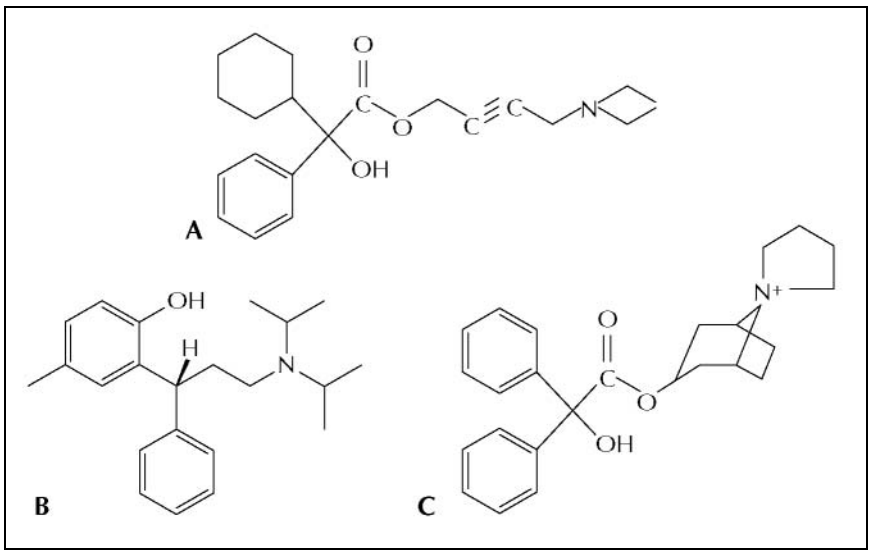

Figure 1. Chemical structures of tertiary amines. **A,** Oxybutynin. **B,** Tolterodine. **C,** Trospium chloride (is a quaternary amine).

easily cross the blood brain barrier. The relative ranking of the amines for lipophilicity and potential ease in crossing the blood brain barrier, from highest to lowest, is darifenacin, oxybutynin/solifenacin, tolterodine, and trospium chloride, according to a theoretical method of calculating the log P and dipole moment of these agents [8]

Muscarinic Receptor Binding Profiles

Studies confirm the existence and potential functions of five unique muscarinic receptor subtypes (M_1–M_5) located throughout the body: M_1, neural tissue; M_2, cardiac and detrusor smooth muscle tissue; M_3, detrusor smooth muscle, salivary glands, and other excretory tissues; M_4, cortex and lung tissue; and M_5, unknown at this time. All of these receptors also are found in the CNS [1,4••,9••,10].

As identified in the literature, subtypes M_2 and M_3 are especially involved in the function of bladder smooth muscle. The M_3 subtype has been found to be the direct mediator of smooth muscle contraction; however, the M_2 subtype opposes sympathetic-mediated smooth muscle contractions. Moreover, it has been proposed that M_2 and M_3 work synergistically to cause a more efficient discharge of urine [2••,6,9••].

A list of the anticholinergic agents used for the treatment of OAB with their respective selectivity for the M_2 and M_3 muscarinic receptor subtypes is provided in Table 1 [3,11,12]. Trospium chloride demonstrates the least specificity of binding to M_2 and M_3 and has the highest overall affinity for all of the M receptor subtypes of the anticholinergic agents used for OAB (Table 1). Binding affinity does not correlate specifically with in vivo activity, but, as noted by Nilvebrant [7], the bladder selectivity of tolterodine has been attributed to a relative nonselectivity of the drug for M_2 versus M_3 receptors compared with oxybutynin.

Bioavailability

The bioavailability of a drug is the fraction of an unchanged drug reaching the systemic circulation after administration by any route [13]. Incomplete absorption is one of the major factors affecting the bioavailability of a drug. Other factors that influence a drug's bioavailability are the effects of food and whether the drug is highly protein-bound. An increased amount of protein binding in the blood (serum) decreases the amount of drug that can be available to the tissues.

As a class, quaternary amines have poor bioavailability with significant intervariability partly because of the hydrophilic nature of the compounds. The poor absorption from the gastrointestinal tract has been documented in studies of the quaternary ammonium compounds ipratropium bromide and hyoscine butylbromide [14,15]. Bioavailabilities range from 0.48% for oxitropium bromide to 11% for trospium chloride [16–18], with most studies reporting 10% orally.

Bioavailability of the tertiary amines can be much higher than that of the quaternary amines. For example, tolterodine reports a bioavailability of up to 74% [19].

Although the bioavailability of the quaternary amines tends to be low when compared with that of the tertiary amines, this can be overcome by increasing the dose, without increasing adverse events, and not taking the drug with food.

Metabolism

The cytochome P450 enzymes are the major catalysts for drug metabolism reactions such as oxidation or reduction. Drugs that are metabolized by the same P450 enzymes will competitively interact with each other for a binding site on the enzyme. The drug with the higher affinity for the active site will be metabolized more efficiently than the lower-affinity drug, thereby potentially altering its absorption, distribution, or elimination and possibly resulting in an

Table 1. Affinity of anticholinergic agents for muscarinic receptor subtypes M_2 and M_3

Agent	M_1	M_2	M_3
Trospium chloride	9.1	9.2	9.3
Tolterodine	8.8	8	8.5
Oxybutynin	8.7	7.8	8.9
Darifenacin	8.2	7.4	9.1
Solifenacin	7.6	6.9	8

Data from Ensing *et al.* [18], Brynne *et al.* [19], and Oxybutynin prescribing information [20].

increase or decrease of the drug at the active site. These drug-drug interactions can be a significant problem for patients who take multiple medications.

Oxybutynin and tolterodine are significantly metabolized by the cytochrome P450 enzymes: oxybutynin by CYP3A4 and tolterodine by CYP2D6 [19,20]. Approximately 7% to 10% of white people are CYP2D6-deficient, potentially resulting in large differences in disposition of drug among patients [21]. However, trospium chloride demonstrates minimal P450 metabolism [22]. This lack of P450 metabolism markedly reduces the potential for drug-drug interactions with trospium chloride.

In addition, approximately 80% of the active parent compound of trospium chloride is excreted unchanged in the urine; however, less than 5% of the active compound of oxybutynin or tolterodine is excreted in the urine. The accumulation of trospium chloride in the bladder may result in a more focused delivery of active compound to the bladder and an additional therapeutic action, while potentially explaining the lack of systemic side effects and enhanced tolerability observed with this agent compared with the others [23]. Studies investigating the intravesical administration of anticholinergic agents directly into the bladder have reported reduced adverse events [24–26]. Further studies are needed to separate the systemic from local effects of these agents.

Half-life

The half-life (t½) of a drug is the time required to change the amount of drug in the body by 50% during elimination [13]. The extended-release formulation of oxybutynin has a t½ of 13.2 hours [20], tolterodine has a t½ of 8.4 hours [21], and the t½ of trospium chloride is 12 to 18 hours [27]. The amount of drug available partly depends on its t½ and its dosing schedule. The therapeutic index of trospium chloride administered twice daily supports its use in comparison with existing agents [28]. In addition, its t½ makes it an ideal compound for incorporation into an advanced delivery system. Propantheline is the only other quaternary amine that has been considered for OAB therapy. Although it has attributes that are similar to those of trospium chloride, a molecular weight of 448 Daltons, and favorably low lipophilicity, it is not a suitable drug option because of its very short t½ (1.6 hours). This would necessitate upward of six to eight doses daily to maintain therapeutic blood serum levels [29].

Onset of Action

The onset of action of trospium chloride has been reported to be approximately 3 days and maximum clinical effect is seen between 3 and 7 days after the initiation of treatment [30]. A placebo-controlled study of the efficacy of trospium chloride in reducing the daily frequency of micturitions and episodes of urinary incontinence showed significant reductions at weeks 1 and 4 and a significant increase in urine volume voided per micturition in the actively treated group [31].

Efficacy

The efficacy, onset, and safety of trospium chloride are well established through its experience on the market in Europe [32]. New phase 3 US data have been presented in abstract form and continue to demonstrate a favorable efficacy: tolerability ratio [33]. In a 1-month study that directly compared tolterodine (tertiary amine), trospium chloride (quaternary amine), and placebo in patients with OAB, only trospium chloride was shown to significantly reduce the number of incontinence episodes (change from baseline was -1.6 for placebo, -1.8 for tolterodine, and -2.9 for trospium chloride, $P < 0.05$). In addition, the micturition frequency, when compared with that of placebo, was significantly reduced with trospium chloride ($P < 0.01$), not with tolterodine [28].

Safety

Anticholinergic agents as a class are classically identified by various systemic anticholinergic effects when administered orally. Effects of particular importance and occurring most commonly in patients treated for OAB symptoms include (in order of frequency) xerostomia, altered visual accommodation, and gastrointestinal transit effects. However, in the elderly population, one of the most debilitating and serious side effects is that of CNS involvement. Confusion and altered mental status changes may prevent elderly patients from using anticholinergic agents altogether. Furthermore, anticholinergic therapy is contraindicated in patients with various diseases, such as narrow-angle glaucoma, tachyarrhythmias, ulcerative colitis, myasthenia gravis, achalasia, and gastrointestinal obstruction [4••,34].

When anticholinergic agents are grouped according to chemical structure as tertiary or quaternary amines, differences in their ability to produce negative systemic effects become apparent. Two studies directly compared oxybutynin (tertiary amine) with trospium chloride (quaternary amine) for use in patients with detrusor hyper-reflexia. Of the 95 patients evaluated in the study by Madersbacher *et*

al. [31], more patients treated with oxybutynin experienced severe dry mouth than those treated with trospium chloride (23% vs 4%). In addition, more oxybutynin-treated patients dropped out of the study than did trospium chloride-treated patients (16% after an average of 7 days vs 6% after an average of 14 days). In a study by Osca-Garcia *et al.* [35] that included 67 patients, significantly more patients treated with oxybutynin experienced dry mouth than those treated with trospium chloride (58.3% vs 29%, $P < 0.01$). In a third study, Halaska *et al.* [36] compared long-term treatment (52 weeks) with oxybutynin and trospium chloride in patients with urge syndrome. "Very good tolerability" was reported in 63% of patients treated with trospium chloride when compared with the same effect in 42% of the oxybutynin group ($P = 0.004$).

Several studies have been conducted to evaluate the CNS adverse effects of anticholinergic agents. In a study by Pietzko *et al.* [37], healthy volunteers were treated with oral oxybutynin, oral trospium chloride, or intravenous trospium chloride. CNS effects were measured using topographic-quantitative electroencephalogram (qEEG) under various conditions for six frequency ranges. Oxybutynin-induced effects (when compared with pretreatment measurements) were statistically significant during the eyes-open and reaction-time periods and highly significant during the eyes-closed period. However, trospium chloride produced no remarkable changes in the EEG recordings when compared with pretreatment measurements. The authors concluded that, because trospium chloride is a quaternary amine, it is unlikely to cross the blood brain barrier and induce CNS adverse effects compared with oxybutynin. Todorova *et al.* [38•] compared the effects of oxybutynin, tolterodine, and trospium chloride on CNS events using qEEG in 64 healthy men under three different conditions: eyes open, eyes closed, and mental demand. The subjective tolerability showed no differences among groups. Trospium chloride and tolterodine did not induce changes in qEEG power in five of six frequency bands; oxybutynin caused significant power reductions in four frequency bands, indicating that oxybutynin crosses the blood brain barrier and can have cognitive effects. Herberg [39] compared the effects of oxybutynin, propiverine, tolterodine, or trospium chloride on CNS parameters, including concentration ability, motor coordination, reaction capability under stress, vigilance, and precision of visual orientation. Their results show that patients treated with trospium chloride and placebo had unimpaired performance abilities in these areas compared with those patients treated with the other anticholinergic agents evaluated. In comparison, inferior results were obtained in some performance tests, particularly vigilance and concentration, from patients treated with oxybutynin, propiverine, and tolterodine.

Conclusions

Trospium chloride, a quaternary amine that has been approved for use in most of Europe and Asia, has been administered in Germany for more than 20 years and has been studied in more than 10,000 patients. When compared in parallel with the two most widely used anticholinergic agents (and tertiary amines) in the United States, oxybutynin and tolterodine, trospium chloride has several theoretic advantages. Based on current data, trospium chloride has not been shown to cause CNS or cognitive dysfunction, presumably because it does not cross the blood brain barrier. In addition, trospium chloride is not highly protein-bound and is not metabolized by the P450 enzyme system, thereby significantly reducing the potential for drug-drug interactions. From a scientific perspective, the perceived advantages of receptor binding, bioavailability, and lipophilicity must be correlated with clinical improvement. Clinical investigations with EEG need further correlation with subclinical or clinical effects. Head-to-head crossover studies will be necessary to truly evaluate the relative efficacy and tolerability of these agents in the clinical setting.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Friebe TP, Mutschler E, Lambrecht G: **Muskarinrezeptor-subtypen: pharmakologische charakterisierung, molekulare struktur lokglisation, function und receptor-effector-kopplung.** *Pharm Z Wiss* 1993, **1:**3–11.
2. •• Igawa Y: **Discussion: functional role of M1, M2, and M3 muscarinic receptors in overactive bladder.** *Urology* 2000, **55(suppl 5A):**47–49.

Provides data on muscarinic receptor research and discusses the significance of receptor subtypes and effects on OAB pharmacotherapy.

3. Ikeda K, Kobayashi S, Suzuki M, *et al.*: **M(3) receptor antagonism by the novel antimuscarinic agent solifenacin in the urinary bladder and salivary gland.** *Naunyn Schmiedebergs Arch Pharmacol* 2002, **366:**97–103.
4. •• Schwantes U, Topfmeier P: **Importance of pharmacological and physiochemical properties for tolerance of antimuscarinic drugs in the treatment of detrusor instability and detrusor hyperreflexia: chances for improvement of therapy.** *Int J Clin Pharmacol Ther* 1999, **37:**209–218.

Reviews and highlights the importance of chemical structure in kinetic and dynamic properties.

5. •• Yoshimura N, Chancellor MB: **Current and future pharmacological treatment for overactive bladder.** *J Urol* 2002, **168:**1897–1913.

Comprehensive review of current research in OAB etiology and treatment. Projections of future avenues of therapy.

6. Schmidt T, Widmer R, Pfeiffer A, *et al.*: **Effect of the quaternary ammonium compound trospium chloride on 24 hour jejunal motility in healthy subjects.** *Gut* 1994, **35:**27–33.
7. Nilvebrant L: **The mechanism of action of tolterodine.** *Rev Contemp Pharmacother* 2000, **11:**13–27.
8. LaVoie: **Personal communication,** 2003.

9.•• Dmochowski RR, Appell RA: **Advancements in pharmacologic management of the overactive bladder.** *Urology* 2000, **56(suppl 6A):**41–49.
Cutting-edge analysis of pharmacologic therapy by leading minds in urology.
10. Hoffman BB, Lefkowitz RJ, Taylor P: **Neurotransmission: the autonomic and somatic motor nervous system.** In *Goodman & Gilman's The Pharmacological Basis of Therapeutics,* edn 9. Edited by Hardman JG, Limbird LE. New York: McGraw-Hill Health Professions Division; 1996:105–139.
11. Eglen RM, Watson N: **Selective muscarinic receptor agonists and antagonists.** *Pharmacol Toxicol* 1996, **78:**59–68.
12. Wallis RM, Napier CM: **Muscarinic antagonists in development for disorders of smooth muscle function.** *Life Sci* 1999, **64:**395–401.
13. Napier C, Gupta P: **Darifenacin is selective for the human recombinant M(3) receptor subtype.** www.icsoffice.org/publications/2002/pdf/4445.pdf. Accessed April 17, 2003.
14. Holford NH, Benet LZ: **Pharmacokinetics and pharmacodynamics: dose selection and the time course of drug action.** In *Basic and Clinical Pharmacology,* edn 7. Edited by Katzung BG. Stamford, CT: Appleton & Lange; 1998:40.
15. Adlung VJ, Höhle KD, Zeren S, *et al.*: **Studies on pharmacokinetics and biotransformation of ipratropium bromide in man.** *Arzneimittelforschung/ Drug Res* 1976, **26:**1005–1010.
16. Hellström K, Rosén A, Söderlund K: **The gastrointestinal absorption and the excretion of H3-butylscopolamine (hyoscine butylbromide) in man.** *Scand J Gastroenterol* 1970, **5:**585–592.
17. Schladitz-Keil G, Spahn H, Mutschler E: **Determination of the bioavailability of the quaternary compound trospium chloride in man from urinary excretion data.** *Arzneimittelforschung/ Drug Res* 1986, **36:**984–987.
18. Ensing K, de Zeeuw RA, Hout WG, *et al.*: **Application of a radioreceptor assay in a pharmacokinetic study of oxitropium bromide in healthy volunteers after single i. v., oral, and inhalation doses.** *Eur J Clin Pharmacol* 1989, **37:**507–512.
19. Brynne N, Stahl MM, Hallen B, *et al.*: **Pharmacokinetics and pharmacodynamics of tolterodine in man: a new drug for the treatment of urinary bladder overactivity.** *Int J Clin Pharmacol Ther* 1997, **35:**287–295.
20. *Oxybutynin chloride (Ditropan® XL) prescribing information.* Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ.
21. *Tolterodine tartrate (Detrol® LA) prescribing information.* Pharmacia Corporation, Peapack, NJ.
22. Beckmann-Knopp S, Rietbrock S, Weyhenmeyer R, *et al.*: **Inhibitory effects of trospium chloride on cytochrome P450 enzymes in human liver microsomes.** *Pharmacol Toxicol* 1999, **85:**299–304.
23. *Scientific monograph, Spasmo-lyt.® (trospiumchlorid) 1999.* Cologne, Germany; Madaus AG,.
24. Madersbacher H, Knoll M: **Intravesical application of oxybutynine: mode of action in controlling detrusor hyperreflexia: preliminary results.** *Eur Urol* 1995, **28:**340–344.
25. Walter P, Grosse J, Bihr AM, *et al.*: **Bioavailability of trospium chloride after intravesical instillation in patients with neurogenic lower urinary tract dysfunction: a pilot study.** *Neurourol Urodyn* 1999, **18:**447–453.
26. Fröhlich G, Burmeister S, Wiedemann A, *et al.*: **Intravesical trospium chloride, oxybutynin, and verapamil for relaxation of detrusor muscle: a placebo-controlled, randomized clinical trial.** *Arzneimittelforschung/Drug Res* 1998, **48:**486–491.
27. Füsgen I, Hauri D: **Trospium chloride: an effective option for medical treatment of bladder overactivity.** *Int J Clin Pharmacol Ther* 2000, **38:**223–234.
28. Jünemann KP, Al-Shukri S: **Efficacy and tolerability of trospium chloride and tolterodine in 234 patients with urge-syndrome: a double-blind, placebo-controlled, multicentre clinical trial (Abstract 85B).** *Presented at the 30th Annual Congress of the International Continence Society.* Tampere, Finland: August 28–30, 2000.
29. *Propantheline bromide (Pro-Banthine®) prescribing information. Physicians Desk Reference®.* Montvale, NJ: Medical Economics Company, Inc.; 1987:1892–1893.
30. Wiedemann A, Schaefer R, Juenemann K: **The onset of treatment effects in anticholinergic drug treatment by trospium chloride: results of a survey in 2553 patients (Abstract 219).** *Presented at the 32nd Annual Congress of the International Continence Society.* Heidelberg, Germany: August 28–30, 2002.
31. Madersbacher H, Stöhrer M, Richter R, *et al.*: **Trospium chloride versus oxybutynin: a randomized, double-blind, multicentre trial in the treatment of detrusor hyperreflexia.** *Br J Urol* 1995, **75:**452–456.
32. Höfner K, Oelke M, Machtens S, *et al.*: **Trospium chloride: an effective drug in the treatment of overactive bladder and detrusor hyperreflexia.** *World J Urol* 2001, **19:**336–343.
33. Zinner N, Gittelman M, Harris R, *et al.*: **Trospium chloride improves overactive bladder symptoms: a multicenter phase III trial (Abstract 102509).** *Presented at the Annual Meeting of the American Urological Association.* Chicago, IL: April 29, 2003. http://aua.agora.com/abstractviewer/av_view.asp. Accessed July 23, 2003.
34. Wein AJ: **Pharmacology of incontinence.** *Urol Clin North Am* 1995, **22:**557–577.
35. Osca-Garcia JM, Agullo M, Sugranes J, *et al.*: **A comparison of trospium chloride and oxybutynin in the treatment of hyperactive bladder: a randomized, double-blind study.** *UROD A* 1997, **10:**40–44.
36. Halaska M, Ralph G, Wiedemann A, *et al.*: **Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability.** *World J Urol* 2003, **20:**392–399.
37. Pietzko A, Dimpfel W, Schwantes U, *et al.*: **Influences of trospium chloride and oxybutynin on quantitative EEG in healthy volunteers.** *Eur J Clin Pharmacol* 1994, **47:**337–343.
38.• Todorova A, Vonderheid-Guth B, Dimpfel W: **Effects of tolterodine, trospium chloride, and oxybutynin on the central nervous system.** *J Clin Pharmacol* 2001, **41:**636–644.
Compares the potential CNS adverse effects of tolterodine, oxybutynin, trospium choride, and placebo in a randomized, single-blind, parallel-group with qEEG study. Oxybutynin caused a significantly greater number of EEG changes than did tolterodine or trospium.
39. Herberg KW: **Everyday safety and traffic safety under incontinence medication.** *Med Welt* 1999, **50:**217–222.