the presence of an intra-atrial mass tend to be attributed to more prevalent disorders such as infections, atherosclerosis, and coronary heart disease.[7] Increased life expectancy and the wide use of echocardiography should lead to some rise in cardiac tumor findings in geriatric patients.

Yichayaou Beloosesky, MD
Department of Geriatrics
Menachem Katz, MD
Department of Cardiology

Joseph Grinblat, MD
Department of Geriatrics
Rabin Medical Center
Golda Campus
Sackler School of Medicine
Tel Aviv University
Petach Tikvah, Israel

REFERENCES

1. Wold LE, Lie JT. Cardiac myxomas: A clinicopathologic profile. Am J Pathol 1980;101:219–240.
2. Blondeau P. Primary cardiac tumors: French studies of 533 cases. Thorac Cadriovasc Surg 1990;38(Suppl 2):192–195.
3. Tazelaar HD, Locke TJ, McGregor CG. Pathology of surgically excised primary cardiac tumors. Mayo Clin Proc 1992;67:957–965.
4. Bire F, Roudant R, Chevalier JM et al. Cardiac myxoma in patients over 75 years of age: Report of 19 cases. Arch Mal Coeur Vaiss 1999;92:323–328.
5. Davison ET, Mumford D, Zaman Q et al. Left atrial myxoma in the elderly: Report of four patients over the age of 70 and review of the literature. J Am Geriatr Soc 1986;34:229–233.
6. Akihiro E, Akira O, Toru K et al. Characteristics of 161 patients with cardiac tumors diagnosed during 1993 and 1994 in Japan. Am J Cardiol 1997;79: 1708–1711.
7. Guillet PH, Baconnet CH, Labrousse A et al. Left atrial myxoma in the elderly: Diagnosis by M-mode and bi-dimensional echocardiography. J Am Geriatr Soc 1981;29:451.

ASSOCIATION BETWEEN OXYBUTYNIN AND NEUROPSYCHIATRIC ADVERSE EFFECTS NOT CONFIRMED IN DAILY PRACTICE

To the Editor: Oxybutynin is a tertiary amine ester possessing anticholinergic, spasmolytic, and local-anaesthetic pharmacological properties and is widely used for the treatment of older patients with overactive bladder presenting with frequency, urgency, or urge incontinence.[1] Due to its pharmacological profile and its biochemical properties that permit passage through the blood-brain barrier,[2] oxybutynin can cause neuropsychiatric adverse drug effects (ADEs).[3] Several papers have been published describing case reports and case series of neuropsychiatric effects in older individuals attributed to oxybutynin.[4–7] According to the published case reports, there seems to be a causal relationship between oxybutynin and the occurrence of neuropsychiatric ADEs. Since the evidence is limited to case reports, the incidence of those ADEs caused by oxybutynin under everyday circumstances is not yet known. A way to quantify side effects of drugs is the concept of prescription sequence analysis (PSA), introduced by Petri and coworkers.[8] This method is based on the observation that certain side effects themselves may induce symptoms requiring the prescription of another medication. Thus, an adverse drug reaction can be the indication for the prescription of a new drug, e.g., drug-induced psychosis treated with antipsychotic drugs.

To assess the risk estimate for neuropsychiatric side effects associated with the use of the spasmolytic drug oxybutynin, we performed a retrospective observational follow-up study using PSA. Patients using flavoxate, a noncentrally acting spasmolytic agent, were obtained as the reference group. This investigation incorporated data obtained from 18 collaborating community pharmacies located in the southern part of The Netherlands (Tilburg and surroundings) covering a population of approximately 200,000 inhabitants. Patients taking the spasmolytic drugs oxybutynin and flavoxate were identified, and an anonymous complete drug dispensing history of each patient over a 2-year period was generated in a computer database. First-time users (age >18 years) of oxybutynin or flavoxate were enrolled in the study. Patients were followed until either the end of the study period or the occurrence of one or more of the following neuropsychiatric adverse events, defined as "start" as well as "switch" of a benzodiazepine or "start" with antipsychotic drug therapy. As determined in a previous study, age; gender; use of anti-Parkinson drugs, antidepressants, benzodiazepines, or antipsychotic drugs; and previous use of other spasmolytics were examined as potential confounders.[9] The relative frequency of the occurrence of a neuropsychiatric ADE was estimated using Poisson regression as the incidence density ratio (IDR), in which the incidence density of flavoxate was taken as the baseline. The IDR can be interpreted as a relative risk. In order to adjust for potential confounding data, indicator variables for gender, age, and concomitant drug use were included in the multivariate Poisson regression model.

In total, 742 older patients were registered who received a first-time prescription of oxybutynin or flavoxate during the study period. There were no relevant differences between the demographic characteristics of the study patients. The mean age of the study population was 59 years; older adults age 60 to 97 years constituted the majority (52%).

Table 1 presents the incidence density of all endpoints while exposed to oxybutynin or flavoxate and the IDR for oxybutynin compared with flavoxate. As shown in this table, oxybutynin was clearly not more frequently associated with any of the defined endpoints ($IDR_{adjusted}$ 1.08 95% confidence interval [CI] 0.60–1.92).

We evaluated the risk of neuropsychiatric adverse drug effects contributed to oxybutynin while used in daily clinical practice. The results indicate that use of oxybutynin was not clearly associated with an increased risk of neuropsychiatric adverse events in comparison with flavoxate, a noncentrally acting spasmolytic agent. Our study was based on longitudinal data obtained from daily clinical practice. To our knowledge, no other studies have been published that make a direct comparison between oxybutynin and flavoxate under everyday circumstances. Such direct comparisons are important because, as described previously, therapeutic outcomes like tolerability, safety, and effectiveness need, in addition to clinical trial data, such nonrandomized comparisons.[10]

A limitation of PSA is that not all ADEs will be identified, that is, the absolute risk is likely to be underestimated. Nevertheless, it is unlikely that the degree of misclassification is different between the two groups. Therefore, we feel that the estimate for the relative risk is unbiased and still valid.

Although the reported case reports in the literature suggest that neuropsychiatric side effects can be caused by oxybutynin, our study indicates that such risk is low. In

Table 1. Risk of Neuropsychiatric Events while Exposed to Spasmolytic Agents

Item	Cases	Exposure Period (days)	ID/1000 Exposed Days	Crude IDR	95% CI	Adjusted IDR*	95% CI
Start benzodiazepine							
flavoxate	8	25,969	0.31	1		1	
oxybutynin	16	56,454	0.28	0.92	0.39–2.15	0.94	0.40–2.22
Switch benzodiazepine							
flavoxate	6	7,663	0.78	1		1	
oxybutynin	19	14,439	1.32	1.68	0.67–4.21	1.90	0.66–5.49
Start antipsychotic drugs							
flavoxate	3	32,670	0.09	1		not estimable	
oxybutynin	2	73,413	0.03	0.30	0.05–1.78	not estimable	
Any endpoint							
flavoxate	17	33,470	0.51	1		1	
oxybutynin	37	70,539	0.52	1.03	0.58–1.83	1.08	0.60–1.92

*Adjusted for age, gender, concomitant medication and former use of another spasmolytic drug.
Note: ID = incidence density; IDR = incidence density ratio; CI = confidence interval.

our opinion, current procedures for drug approval still fail to recognize rare adverse drug effects that are of specific importance to older people. Therefore, systematic research is needed to ensure recognition of infrequent adverse effects of medication used in large populations under everyday circumstances.

Kris L.L. Movig, PharmD
Antoine C.G. Egberts, PhD
Albert W. Lenderink, PharmD
Hospital Pharmacy Midden-Brabant
TweeSteden Hospital and St. Elisabeth Hospital
Tilburg, The Netherlands
Department of Pharmacoepidemiology and Pharmacotherapy
Utrecht Institute for Pharmaceutical Sciences
Utrecht University, The Netherlands

Hubert G.M. Leufkens, PhD
Department of Pharmacoepidemiology and Pharmacotherapy
Utrecht Institute for Pharmaceutical Sciences
Utrecht University, The Netherlands

REFERENCES

1. Yarker YE, Goa KL, Fitton A. Oxybutynin: A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in detrusor instability. Drugs Aging 1993;6:243–262.
2. Pietzko A, Dimpfer 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.
3. Katz IR, Sands LP, Bilker W et al. Identification of medications that cause cognitive impairment in older people: The case of oxybutynin chloride. J Am Geriatr Soc 1998;46:8–13.
4. In't Veld BA, Kwee–Zuiderwijk WJM, Puijenbroek van EP et al. Neuropsychiatrische bijwerkingen toegeschreven aan het gebruik van oxybutynine. Ned Tijdschr Geneeskd 1998;142:590–592.
5. Jonville AP, Dutertre JP, Autret E et al. Effets indésirables du chlorure d'oxybutynine (Ditropan). Bilan de l'enquete officielle des Centres Régionaux de Pharmacovigilance. Therapie 1992;47:389–392.
6. Valsecia ME, Malgor LA, Espíndola JH et al. New adverse effect of oxybutynin: "Night terror." Ann Pharmacother 1998;32:506.
7. Donnellan CA, Fook L, McDonald P et al. Oxybutynin and cognitive dysfunction. Br Med J 1997;315:1363–1364.
8. Petri H, De Vet HCW, Naus J et al. Prescription sequence analysis: A new and fast method for assessing certain adverse reactions of prescription drugs in large populations. Stat Med 1988;7:1171–1175.
9. Movig KLL, Egberts ACG, Lenderink AW et al. Selective prescribing of spasmolytics. Ann Pharmacother 2000;34:716–720.
10. Leufkens HG, Urquhart J. Variability in patterns of drug usage. J Pharm Pharmacol 1994;46(Suppl 1):433–437.

CHARLES BONNET SYNDROME AND OPIOIDS

To the Editor: Charles Bonnet Syndrome (CBS) is characterized by the presence of complex visual hallucinations in visually impaired, but otherwise psychologically normal people.[1] Three developmental types of the syndrome can be distinguished, namely episodic, periodic, and continual. We present the case of a cancer patient in whom opioids induced continual CBS, which became episodic through an opioid rotation and haloperidol.

Case report: A 72-year-old man with bone metastases from a prostate carcinoma in terminal phase was examined in our palliative care unit because he was suffering severe pain. The patient had been completely blind from the age of 60, following pigmentary retinitis. Forty-eight hours after starting pain treatment with transdermal fentanyl (25 μg/h) the patient showed high anxiety due to the presence of visual hallucinations, especially during the night. These hallucinations were of a complex nature, such as dwarfs, animals, and small, deformed faces. On being questioned, he admitted that for years he had been suffering from episodes of occasional hallucinations of a simple nature that he never disclosed to his family. The neurological examinations ruled out the presence of delirium and other abnormalities. A cranial computerized tomography taken 1 month before had showed no brain damage. There was no evidence of metabolic disturbances. An opioid rotation to methadone (10 mg/day) was carried out and haloperidol (3 mg/day) was associated. Seven days later, daily hallucinations and pain persisted, so methadone was shifted to 90 mg/day of sustained-release morphine and haloperidol dose was increased to 5.5 mg/day. Five days later the pain was well controlled and a decrease in the frequency of the hallucinations was noticeable. Haloperidol was withdrawn and the patient was discharged. Two later examinations carried out 15 and 30 days afterwards revealed that short-duration hallucination episodes were taking place 2 to 3 days a week.