

Non-Steroidal Anti-Inflammatory Drugs and Antibiotics Prescription Trends at a Central West Bank Hospital

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توجهات وصف العلاج باستخدام مضادات الالتهاب غير الستيرويدية و المضادات الحيوية في مشفى مركزي في الضفة الغربية

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الملخص: الهدف: هدفت هذه الدراسة إلى وصف الاتجاهات السائدة للعيادات الخارجية في وصف مضادات الالتهاب غير الستيرويدية و المضادات الحيوية في مشفى مركزي في الضفة الغربية. الطريقة: في هذه الدراسة الاستيعابية المستعرضة تم التحقق من 2,208 وصفة علاجية صادرة على مدى عام كامل عن العيادات الخارجية و غرفة الطوارئ التابعة لمشفى بيت جالا الحكومي في مدينة بيت لحم بالضفة الغربية. حيث تم تحليل الوصفات من حيث كم و نوع مضادات الالتهاب غير الستيرويدية و المضادات الحيوية الموصوفة و مدى ملاءمة الوصفات للتشخيص الطبي. النتائج: من مجموع الوصفات العلاجية شكلت مضادات الالتهاب غير الستيرويدية 410 وصفة (18.6%)، بما في ذلك ديكلوفيناك (40.2%)، أسبرين قليل الجرعة (23.9%)، ايبوبروفين (17.8%)، إندوميثاسين (15.1%). نسبة قليلة من هذه الوصفات احتوت على توليفة من هذه الأدوية (2.5%). وصفة طبية واحدة فقط احتوت عقارا مثبطا لإنزيم سايلواوكسيجيناز-2 (0.2%). وكان مدى ملاءمة وصف هذه الأدوية للتشخيص كما يلي: مناسب (58.3%)، غير مناسب (14.4%) و غير ممكن التحديد (27.3%). كان معدل استخدام المضادات الحيوية 30.3% (669 من مجموع الوصفات العلاجية). المضادات الحيوية الموصوفة شملت أموكسيسيلين (23.3%)، اوجيمنتين (14.3%)، كوينولون (12.7%)، الجيل الأول والثاني من السيفالوسبورين (9.4% و 12.7%، على التوالي)، وماكروليدات (7.2%). كذلك احتوت ما نسبته 9.4% من الوصفات على أكثر من مضاد حيوي واحد كان أبرزها الجيل الثاني من السيفالوسبورين مع المترونيدازول (4.3%). وكان مدى ملاءمة وصف المضادات الحيوية وفقا للتشخيص كما يلي: مناسب 44.8%، غير ملائم 20.6% و غير ممكن التحديد 34.6% الخلاصة: كشفت هذه النتائج عددا كبيرا نسبيا واستخداما غير ملائم للمضادات الحيوية و مضادات الالتهاب غير الستيرويدية. بناء على ذلك ينبغي تبني برنامج يعزز من معرفة الأطباء بأهمية الوصف المبني على أسس صحيحة لهذه الأدوية.

مفتاح الكلمات: مضادات الالتهاب غير الستيرويدية، المضادات الحيوية، وصفة علاج، فلسطين.

ABSTRACT: Objectives: We aimed to reliably describe the pattern of outpatient prescription of non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics (ATBs) at a central hospital in the West Bank, Palestine. **Methods:** This was a retrospective, cross-sectional study investigating a cohort of 2,208 prescriptions ordered by outpatient clinics and the emergency room over one year in Beit Jala Hospital in Bethlehem, West Bank. The orders were analysed for the rate and types of NSAIDs and ATBs utilised, and the appropriateness of these drugs to the diagnosis. **Results:** Of the total prescriptions, 410 contained NSAIDs (18.6%), including diclofenac (40.2%), low dose aspirin (23.9%), ibuprofen (17.8%) and indomethacin (15.1%). A minority of these prescriptions contained a combination of these agents (2.5%). Only one prescription contained cyclooxygenase-2 inhibitors (0.2%). The appropriateness of NSAID use to the diagnosis was as follows: appropriate (58.3%), inappropriate (14.4%) and difficult to tell (27.3%). The rate of ATB use was 30.3% (669 prescriptions). The ATBs prescribed were amoxicillin (23.3%), augmentin (14.3%), quinolones (12.7%), first and second generation cephalosporins (9.4% and 12.7%, respectively) and macrolides (7.2%). ATB combinations were identified in 9.4%, with the most common being second-generation cephalosporins and metronidazole (4.3%). Regarding the appropriateness of prescribing ATBs according to the diagnosis, it was appropriate in 44.8%, inappropriate in 20.6% and difficult to tell in 34.6% of the prescriptions. **Conclusion:** These findings revealed a relatively large number and inappropriate utilisation of ATBs and NSAIDs. An interventional programme needs to be adopted to reinforce physicians' knowledge of the rational prescription of these agents.

Keywords: NSAIDs; Antibiotics; Prescription; Palestine.

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ADVANCES IN KNOWLEDGE

- *Non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics (ATBs) are over-prescribed at the study hospital in the central West Bank.*
- *A lack of rational utilisation of NSAIDs and ATBs was observed, and this trend may be observed at other institutions as well.*

APPLICATION TO PATIENT CARE

- *Since NSAIDs are potentially toxic drugs, physicians must prescribe them only when strictly indicated and take individual patient risk factors into consideration when selecting certain agents.*
- *Rational prescription of ATBs is extremely important to avoid the spread of potentially life-threatening multi-drug-resistant bacteria. Therefore, physicians must be very careful when prescribing these drugs.*
- *The results may guide interventional programmes focusing on general practitioners and specialists in various clinical settings to improve their prescription habits of these agents.*

NON-STEROIDAL ANTI-INFLAMMATORY drugs (NSAIDs) are widely used worldwide as anti-inflammatory, antipyretic and analgesic agents.¹ Low-dose aspirin, however, is prescribed for both primary and secondary prevention of coronary artery and cerebrovascular diseases (CBVD).^{2,3} Despite their established efficacy, these drugs have a wide range of adverse drug reactions, including but not limited to gastric ulceration and bleeding, bleeding tendencies due to the inhibition of platelet aggregation, nephrotoxicity, and sodium/water retention.⁴⁻⁷ Therefore, and due to differences in the adverse effect profile among various NSAIDs, assessing an individual patient's risk is an important factor when selecting a NSAID.⁸ Agents which selectively inhibit cyclooxygenase-2 enzyme (COX-2 inhibitors), like oxicams and coxibs, are equally effective to non-selective NSAIDs, such as diclofenac and ibuprofen, and lack many of the serious adverse effects of the latter.⁹ Notably, COX-2 inhibitors offer an excellent alternative for patients at risk for serious gastrointestinal (GIT) adverse effects, particularly upper GIT ulceration and bleeding. However, the cardiovascular toxicity associated with COX-2 inhibitors and some other NSAIDs further complicates the choice of therapy.¹⁰ Over the last few decades, the prescription rate of NSAIDs has been on the rise, largely due to an increasingly aged population and the consequent rise in the prevalence of diseases that respond to NSAIDs, particularly infectious and inflammatory conditions.¹¹ Therefore, the utilisation pattern of these drugs and physician awareness of the differences among various NSAIDs needs to be frequently assessed in various clinical settings.¹²

The discovery of antibiotics (ATBs) constituted a revolution in modern medicine. However, like

NSAIDs, they are a first-line weapon against infectious diseases, and therefore are liable to be overused.¹³ Due to the huge consumption rate of broad-spectrum and combination anti-bacterial drugs, many developing countries have experienced unfavourable trends in ATB use and bacterial resistance.¹⁴ The emergence of catastrophic multi-drug-resistant strains is currently receiving a lot of attention due to increasing morbidity, mortality and health costs.¹⁵ The problem is on the rise and the treatment options for combating bacterial resistance are narrowing. Ideally, the rational and cost-effective use of ATBs should be carefully balanced to maximise the clinical therapeutic effect while minimising drug-related toxicity, and the development of new resistant strains and the spread of existing ones.¹⁶ Therefore, to prevent bacterial resistance, many countries worldwide have adopted programmes to reduce ambulatory ATB consumption as part of an international strategy.¹⁷ These include group educational meetings and training, and monitoring and feedback on physician prescribing behaviour and patient education.¹⁸

The present investigation was carried out to provide insight into the prescription rate and trend of NSAIDs and ATBs at a central hospital in the West Bank. The study aimed to improve the rational and cost-effective use of these drugs and comment upon any lacunae in their consumption pattern. The authors speculate that the results of this study will guide interventional programmes focusing on general practitioners and specialists in various clinical settings to improve their prescription habits of these agents.

Methods

The majority of Palestinians residing in the West Bank are entitled to governmental healthcare provided by a network of primary healthcare centres and hospitals. Patients are initially evaluated by a general practitioner at a primary healthcare centre and are referred, if needed, to a specialist at a hospital outpatient clinic (OPC). Emergency cases can be treated at the emergency rooms (ERs) of these hospitals. Most prescriptions originating from primary healthcare centres, OPCs or ERs are dispensed at pharmacies at governmental hospitals. All prescription orders are collected from patients upon dispensation and are kept at hospital pharmacies. The prescription orders contain elements which should be clearly filled by the prescribing physician. These elements include the source of the prescription, the prescriber's name, a patient's details, current diagnosis or diagnoses, and a list of medications with instructions to the pharmacist and patient.

Physicians in the target hospital were not aware of this study. Ethical approval was provided by the Al-Quds University Human Research Ethics Committee. The target hospital was Beit Jala Hospital, which is the central governmental hospital in the Bethlehem District. This area has a population of 140,000 people, making up 7.3% of the population of the West Bank. OPC and ER prescriptions from within the hospital, irrespective of the clinic of origin, received and kept by the Pharmacy Department over a period of one year (20 December 2010–19 December 2011) were analysed retrospectively and systemically. This period was divided into 4 seasons: spring, summer, autumn and winter. In each season, all prescriptions from one randomly selected week (7 days) were analysed. The analysis was carried out from January–March 2012.

All prescriptions containing NSAIDs or ATBs were examined to determine the clinic of origin, number and types of NSAIDs or ATBs ordered, and the appropriateness of utilising these drugs with the stated diagnosis on the prescription order. The appropriateness of the drug treatment to the diagnosis was classified as follows: appropriate when drugs prescribed were related to the diagnosis, inappropriate when the drugs were unrelated to the diagnosis, and difficult to tell when the diagnosis was missing or not clearly written. The use of

NSAIDs was considered appropriate if the patient had experienced fever or pain due to an infectious condition (e.g. upper respiratory tract infection or cholecystitis), musculoskeletal condition (e.g. rheumatoid arthritis, gout, osteoarthritis or muscle stiffness), painful condition (e.g. metastatic bone pain, trauma, migraine headache, dysmenorrhoea, postoperative pain or renal colic), or the prophylaxis of ischemic heart disease or CBVD (for low-dose aspirin only).

On the other hand, the use of NSAIDs was considered inappropriate if the physician prescribed a combination of more than one NSAID in the same order, or if the diagnosis stated on the prescription order contained one of the following conditions: peptic ulcer disease, gastroenteritis, non-specific abdominal pain or colic, diarrhoea, pregnancy, renal failure, heart failure, asthma or chronic obstructive pulmonary disease (COPD). For ATB-containing prescriptions, the treatment was considered appropriate if the diagnosis appearing on the prescription order included any infectious bacterial conditions such as a urinary tract infection, meningitis, cellulitis, pneumonia, etc. However, treatment with ATBs was labeled inappropriate if the patient was given a diagnosis which most likely was not a bacterial infection, such as viral infections (gastroenteritis or viral upper respiratory tract infections such as nasopharyngitis, but not otitis media or tonsillitis, which are commonly caused by bacteria). Similarly, ATB prophylaxis was considered unindicated if ATBs were prescribed for normal spontaneous vaginal deliveries, or non-specific abdominal pain or colic. It is worth emphasising that the aim was to examine the appropriateness of using ATBs, not to judge the selection of a certain ATB for a certain patient.

The data were examined using the Statistical Package for the Social Sciences (SPSS), Version 17 (IBM Corp., Chicago, Illinois, USA), and simple descriptive statistics were utilised to analyse the results.

Results

The sample was comprised of 2,208 prescription orders. The majority of the prescriptions were issued by the OPCs (90.3%) followed by the ER (7.8%) while in the rest the source was missing (1.9%). The number of drugs included in the

Table 1: Frequency of non-steroidal anti-inflammatory drug prescriptions according to type and clinic of origin in a central hospital in the West Bank (n = 410)

	Prescriptions (n)	Frequency (%)
Type of NSAID prescribed		
Diclofenac	165	40.2
Low-dose aspirin	98	23.8
Ibuprofen	73	17.8
Indomethacin	62	15.1
COX-2 inhibitors	1	0.2
Others	1	0.2
Combination NSAIDs	10	2.7
Source of NSAID prescriptions		
Orthopaedics	136	33.2
Medicine	103	25.1
Oncology	55	13.4
Surgery	41	10.0
ER	33	8.0
Obstetrics/Gynaecology	9	2.2
Paediatrics	1	0.2
Other	32	7.8

NSAID = non-steroidal anti-inflammatory drug;
COX = cyclooxygenase; ER = Emergency Room.

prescriptions ranged from 1–9, but the majority (90.4%) contained 3 or fewer drugs. The distribution of the prescriptions by season was as follows: winter (30.6%), spring (17.5%), summer (35.6%) and autumn (16.3%). Based on the clinic of origin, 30.4% of the prescriptions were sent by the Oncology Clinic, followed by the Departments of Internal Medicine (21%), Orthopaedics (9.5%), Surgery (9%), ER (7.8%), Paediatrics (6.6%) and Obstetrics/Gynaecology (6.3%).

The NSAID utilisation pattern was examined in this study [Table 1]. Out of the 2,208 prescriptions analysed, 410 contained NSAIDs (18.6%). Diclofenac was the most commonly prescribed agent (40.2%), followed by low-dose aspirin (27.3%), ibuprofen (17.8%) and indomethacin (15.1%). Only one prescription contained COX-2 inhibitor NSAIDs (0.2%). Combination NSAIDs were identified in a minority of prescriptions (2.8%). The pattern of prescribing NSAIDs was further analysed for the source of the prescription and the appropriateness of the prescription to the diagnosis. The clinic of

Table 2: Frequency of antibiotic prescription according to type and clinic of origin in a central hospital in the West Bank (n = 669)

	Prescriptions (n)	Frequency (%)
Type of ATB prescribed		
Amoxicillin	156	23.3
Augmentin	96	14.3
Quinolones	85	12.7
Second-generation cephalosporins	85	12.7
First-generation cephalosporins	63	9.4
Macrolides	48	7.2
Metronidazole	25	3.7
Other ATBs	111	16.7
*Combination ATBs	58	9.4
Source of ATB prescriptions		
Orthopaedics	32	4.8
Medicine	108	16.1
Oncology	70	10.5
Surgery	132	19.7
ER	89	13.3
Obstetrics/Gynaecology	99	14.8
Paediatrics	64	9.6
Other	75	11.2

*Combination ATBs do not count as part of the total number of ATBs analysed since these prescriptions included more than one ATB.

ATB = antibiotic; ER = Emergency Room.

origin of NSAIDs-prescription was as follows: the Departments of Orthopaedics (33.2%), Internal Medicine (25.1%), Oncology (13.4%), Surgery (10%), ER (8%), Obstetrics/Gynaecology (2.2%) and Paediatrics (0.5%). The appropriateness of NSAIDs use to the diagnosis was as follows: appropriate (58.3%), inappropriate (14.4%) and difficult to tell (27.3%).

Regarding the prescription trend of ATBs [Table 2], the proportion of outpatient prescriptions which generated ATBs was 30.3% (669 prescriptions). Amoxicillin was the ATB most often prescribed (23.3%), followed by augmentin (14.3%), quinolones (12.7%), first- and second-generation cephalosporins (9.4 and 12.7%, respectively) and macrolides (7.2%). ATB combinations were identified in 9.4% of the prescriptions, with the most common

being second-generation cephalosporins and metronidazole (4.3%). The General Surgery Clinic was the most frequent source of ATBs (19.7%), followed by the Departments of Internal Medicine (16.1%), Obstetrics/Gynaecology (14.8%), ER (13.3%), Oncology (10.5%), Paediatrics (9.6%) and Orthopaedics (4.8%). Regarding the appropriateness of prescribing ATBs to the diagnosis, it was appropriate in 44.8%, inappropriate in 20.6%, and difficult to tell in 34.6% of the orders.

Discussion

This investigation targeted a cohort of 2,208 outpatient prescriptions issued at a central hospital in the West Bank to evaluate the amount and pattern of outpatient prescriptions of NSAIDs and ATBs. The data analysis in the present study revealed a large number and inappropriate prescriptions of NSAIDs and ATBs. Results of this study may help address issues related to the prescription pattern of these drugs, especially in the ambulatory setting.

Almost one-fifth of the prescriptions contained NSAIDs, emphasising a high tendency towards utilising these drugs, as previously reported.¹⁹ The most commonly prescribed NSAID was found to be diclofenac, accounting for more than 40% of the prescriptions, followed by ibuprofen and indomethacin. Only one prescription (0.2%) contained COX-2 inhibitors. Notably, a tendency towards prescribing diclofenac, with its high GIT bleeding risk, over other relatively GIT-tolerable NSAIDs like ibuprofen, and COX-2 inhibiting agents was highlighted in this study.²⁰ This notion emphasises limited physician attention to the importance of considering individual patients' gastrointestinal (GI) risk factors when selecting NSAIDs. There are variations among countries in the selection trend of NSAIDs. In concert with these findings, a recent study in Serbia reported that the most commonly prescribed NSAID was diclofenac followed by ibuprofen.²¹ However, in Sweden the most commonly prescribed NSAID was the COX-2 inhibitor rofecoxib.²² A similar pattern was reported in Australia where non-selective NSAID-prescribing decreased while COX-2 inhibitor utilisation increased from 1997 to 2006.²³

Regarding the appropriateness of prescribing NSAIDs to the diagnosis, this study found that approximately 60% of the prescriptions were

appropriate, whereas 14.4% were inappropriate. These findings are far worse than those reported by Irshaid et al., who showed that in a teaching hospital in Saudi Arabia a minority of outpatient NSAID prescriptions (4.2%) were inappropriate.²⁴ Adams et al. reported a high prevalence of inappropriate use of NSAIDs in Australia among patients with hypertension (16%), kidney disease (15.9%) and a history of CBVD (20%).²⁵ Due to the differences in adverse effects among NSAIDs, awareness about the rational utilisation and appropriate selection of these drugs for each individual patient needs to be strongly emphasised. Moreover, physician awareness of the efficacy and safety of COX-2 inhibitors and paracetamol as alternatives to NSAIDs needs to be reinforced.

This study's findings regarding the prescription pattern of ATBs raise concerns about the high rate and irrational use of these drugs. We report that the average prevalence of ATB prescription was very high, with a frequency touching 30.3%. The use of the extended-spectrum penicillins amoxicillin and augmentin accounted for more than one-third while the use of combination ATBs was seen in one-tenth of the ATB-containing prescriptions in this sample. We also found that ATBs were used inappropriately in one-fifth of prescriptions. Haphazard use of ATBs has caused these essential drugs to lose their effectiveness due to emerging bacterial resistance. In the developing world, the problem is complex, involving inadequate access to more effective ATBs along with an inadequate capability to use them appropriately. Both circumstances may result in the rapid spread of antimicrobial resistance, which significantly increases the risk of morbidity and mortality. To combat the overuse and misuse of ATBs, suitable and sustainable interventions should be introduced to raise physician awareness about the importance of prescribing ATBs rationally and cost-effectively.

This study has certain limitations which should be taken into consideration when interpreting these findings. In our setting, this investigation was not an accurate measure of the exposure of the West Bank population to NSAIDs and ATBs since our sample was taken from only one hospital. A larger-scale study involving samples of prescriptions from the several public and private hospitals in the West Bank will be needed to measure trends in the use of these drugs as part of a national surveillance system.

Moreover, when we evaluated the appropriateness of NSAID and ATB utilisation to the diagnosis, we relied on the outpatient prescription order rather than the patient's files. An examination of the files would have provided more detailed information concerning the patient's condition(s) and the appropriateness of the prescription. Finally, this study focused on the outpatient prescription trends of NSAIDs and ATBs whereas no data were collected about this trend in the inpatient setting.

Conclusion

In summary, a high rate of outpatient prescription and irrational utilisation of NSAIDs and ATBs was reported. These findings emphasise the need for physician educational interventions concerning the rational prescription of NSAIDs and ATBs. National guidelines on the appropriate utilisation of these drugs are urgently warranted to improve the situation. However, the key to success in this endeavor would be strong physician commitment, patient education and governmental support.

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References

- Middleton C. Non-steroidal anti-inflammatory drugs: Indications for use. *Nurs Times* 2003; 99:30–2.
- Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: A sex-specific meta-analysis of randomized controlled trials. *JAMA* 2006; 295:306–13.
- Berger JS, Brown DL, Becker RC. Low-dose aspirin in patients with stable cardiovascular disease: A meta-analysis. *Am J Med* 2008; 121:43–9.
- García Rodríguez LA, Hernández-Díaz S. Relative risk of upper gastrointestinal complications among users of acetaminophen and nonsteroidal anti-inflammatory drugs. *Epidemiology* 2001; 12:570–6.
- Amer M, Bead VR, Bathon J, Blumenthal RS, Edwards DN. Use of nonsteroidal anti-inflammatory drugs in patients with cardiovascular disease: A cautionary tale. *Cardiol Rev* 2010; 18:204–12.
- Musu M, Finco G, Antonucci R, Polati E, Sanna D, Evangelista M, et al. Acute nephrotoxicity of NSAID from the foetus to the adult. *Eur Rev Med Pharmacol Sci* 2011; 15:1461–72.
- Stichtenoth DO, Frolich JC. COX-2 and the kidneys. *Curr Pharm Des* 2000; 6:1737–53.
- Adebajo A. Non-steroidal anti-inflammatory drugs for the treatment of pain and immobility-associated osteoarthritis: Consensus guidance for primary care. *BMC Fam Pract* 2012; 13:23.
- Kivitz AJ, Moskowitz RW, Woods E, Hubbard RC, Verburg KM, Lefkowitz JB, et al. Comparative efficacy and safety of celecoxib and naproxen in the treatment of osteoarthritis of the hip. *J Int Med Res* 2001; 29:467–79.
- Scheiman JM, Sidote D. Which NSAID for your patient with osteoarthritis? *J Fam Pract* 2010; 59:E1–6.
- Krajcik S, Bartosovic I. [Non-steroidal anti-inflammatory drugs in the elderly]. *Vnitr Lek* 2000; 46:360–4.
- Paul AD, Chauhan CK. Study of usage pattern of nonsteroidal anti-inflammatory drugs (NSAIDs) among different practice categories in Indian clinical setting. *Eur J Clin Pharmacol* 2005; 60:889–92.
- McKay RM, Vrbova L, Fuertes E, Chong M, David S, Dreher K, et al. Evaluation of the Do Bugs Need Drugs? program in British Columbia: Can we curb antibiotic prescribing? *Can J Infect Dis Med Microbiol* 2011; 22:19–24.
- Takeshita N. [Travellers and multi-drug resistance bacteria]. *Nihon Rinsho* 2012; 70:324–8.
- Coker RJ, Hunter BM, Rudge JW, Liverani M, Hanvoravongchai P. Emerging infectious diseases in southeast Asia: Regional challenges to control. *Lancet* 2011; 377:599–609.
- Ison CA. Antimicrobial resistance in sexually transmitted infections in the developed world: Implications for rational treatment. *Curr Opin Infect Dis* 2012; 25:73–8.
- Steciwko A, Lubieniecka M, Muszynska A. [Antibiotics in primary care]. *Pol Merkur Lekarski* 2011; 30:323–6.
- Smeets HM, Kuyvenhoven MM, Akkerman AE, Welschen I, Schouten GP, van Essen GA, et al. Intervention with educational outreach at large scale to reduce antibiotics for respiratory tract infections: A controlled before and after study. *Fam Pract* 2009; 26:183–7.
- Hungin AP, Kean WF. Nonsteroidal anti-inflammatory drugs: Overused or underused in

- osteoarthritis? *Am J Med* 2001; 110:8S–11S.
20. Rainsford KD. Ibuprofen: Pharmacology, efficacy and safety. *Inflammopharmacology* 2009; 17:275–342.
 21. Mijatovic V, Calasan J, Horvat O, Sabo A, Tomic Z, Radulovic V. Consumption of non-steroidal anti-inflammatory drugs in Serbia: A comparison with Croatia and Denmark during 2005–2008. *Eur J Clin Pharmacol* 2011; 67:203–7.
 22. Vlahovic-Palcevski V, Wettermark B, Bergman U. Quality of non-steroidal anti-inflammatory drug prescribing in Croatia (Rijeka) and Sweden (Stockholm). *Eur J Clin Pharmacol* 2002; 58:209–14.
 23. Barozzi N, Sketris I, Cooke C, Tett S. Comparison of nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 (COX-2) inhibitors use in Australia and Nova Scotia (Canada). *Br J Clin Pharmacol* 2009; 68:106–15.
 24. Irshaid YM, Al-Homrany MA, Hamdi AA. A pharmacoepidemiological study of prescription pattern for upper respiratory infections in a tertiary health care center. *Saudi Med J* 2005; 26:1649–51.
 25. Adams RJ, Appleton SL, Gill TK, Taylor AW, Wilson DH, Hill CL. Cause for concern in the use of non-steroidal anti-inflammatory medications in the community—A population-based study. *BMC Fam Pract* 2011; 12:70.